HEMOCHROMATOSIS BY JOSEPH T BEARDWOOD JR AND GEORGE P ROUSE JR THIS YEAR BOOK PAGE 675

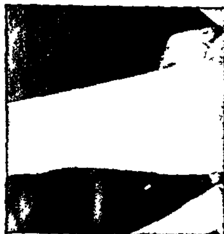


FIG 1

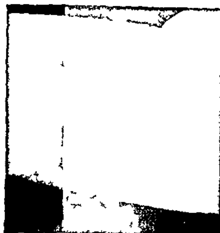


FIG 2

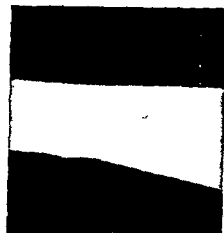


FIG 3



FIG 4



FIG 5

F G 1 —C t ol sk te t 10 m afte nj ct n FIG 2 —Control k test 30 m n after j ct on FIG 3.—Contr l k n test 1 hr after j ect on FIG 4 —Case 2 sk n te t po t fte 1 h FIG 5 —C se 1 sk n te t pos t ve afte 1 h

THE 1945 YEAR BOOK *of* GENERAL MEDICINE

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This volume is one of the 12 comprising the Practical Medicine Series of Year Books founded in 1900 by G P Head M D., and C. J Head and published continuously since then The complete list follows

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Diseases of the Digestive System and of Metabolism

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PART I

INFECTIOUS DISEASES

COMMON COLD

Common Cold Not Caused by Virus Edward E Brown[1] (M C A U S) presents evidence showing that a virus causes relatively few colds and that the hemolytic streptococcus is the more common cause of the common cold Data include observations made over 13 years on children with frequent colds and on children with rheumatic fever and allergy When an attempt was made to determine whether children with rheumatic fever had colds or not it was found on the basis of 22 clinical signs that all had chronic suppurative sinusitis Experimental work reported by Dochez and his co workers on chimpanzees showed that a period of immunity of three to four months follows a cold caused by a virus Yet it was common to find a child with six or eight colds in four months among the rheumatic and bronchitic children studied The conclusion is therefore reached that if one of these colds was due to a virus the remaining five or seven colds must have been due to other causes A few of these remaining colds could be traced to allergic insults but most of them seemed to exist during rapid changes of weather at a time when colds were prevalent throughout the city

Streptococcic dissociation i e change from the more virulent to the less virulent types of the organism in the body by successful defense mechanisms seems to account for the presence of Streptococcus viridans in the pharynx of adults This dissociant has also been found in

(1) N thw t Med. 44 9 40 F b y 1945

Dengue Fever is discussed by David Q Ewing[3] (M C A U S) It is characterized by precipitous onset of chilliness dizziness fever prostration headache and severe aching of legs back and arms Within a few hours postorbital pain develops accentuated by eye movements there are also hypersensitivity and itching of the skin anorexia perverted taste and smell vomiting and constipation or diarrhea Examination reveals an erythematous blush and puffiness of the face reddened soft palate and anterior faucial pillars and occasional enlarged cervical lymph nodes Remissions with subsidence of fever and symptoms occur on the third day and last several hours to two days The second rise of temperature giving the typical saddle back curve is brief but accompanied by recurrence of severe aching an erythematous morbilliform rash and an intractable itching and rosy blush of the palms and soles Blood counts show leukopenia with relative lymphocytosis Convalescence is slow 7–10 days elapsing before patients can be returned to duty and characterized by mental depression and physical weakness

Treatment is supportive aspirin and morphine for pain and intravenous fluid if necessary A light weight black cloth over the eyes may relieve postorbital aching Sedatives are ineffective

Dengue has an incubation period of 7–10 days is caused by a filtrable virus and is transmitted by Aedes aegypti Immunity after attacks varies from a few months to a few years Epidemiology is characterized by explosive epidemics incapacitating great proportions of the population

Production of Immunity to Dengue with Virus Modified by Propagation in Mice Albert B Sabin and R Walter Schlesinger[4] (Children s Hosp , Cincinnati) report successful propagation of dengue virus in mice by

(3) M Clin. N th Amer ca 28 1471 1483 N emb 1944
(4) S i 101 640 642 J n 22 1945

routine cultures of material from children with frequent colds Sewall states that this organism is furnished to the pharynx by chronic sinusitis and that it and other variants of the hemolytic streptococcus reside in many sinuses Streptococcus viridans, growing on sinus mucous membranes becomes activated either at expiration of immunity in the host or after chilling of the body A conversion into the hemolytic streptococcus then occurs Penetration of this organism into the sinus mucosa sets off the humoral defense Leukocytes extrude attenuated dissociants usually in greater numbers than the hemolytic streptococcus Thus the active and complicated process known as the common cold is produced Brown believes that such colds probably constitute well over 90 per cent of the colds observed among children with rheumatic fever and with chest conditions They are the usual common cold found in cold susceptible children and adults and the more common predisposing factor is chilling of the body

[Our own bacteriologic examinations do not support Brown s statement that the hemolytic streptococcus is a common cause of colds It is probable that the frequent colds described are not colds at all but exacerbations of chronic nasal infection. It is also probable that the role of streptococci in colds is that of a secondary infection —Ed]

Use of Vaccines for Common Cold is still experimental and of unproved effectiveness according to the status report of the Council on Pharmacy and Chemistry and the Council on Industrial Health of the American Medical Association Vaccines consist of killed bacteria obtained originally from the upper respiratory tract and combined in various proportions They have been administered orally parenterally and by spray with highly publicized apparently good results However the variability of colds in severity and frequency and of reactions to them makes individual case reports unreliable Controlled studies have been inadequate or unencouraging

[Certainly the benefit from cold vaccines is so questionable that their use seems hardly worth while —Ed]

(2) J A M A 126 895 897 Dec 2 1944

and petechiae did not appear The nine volunteers all became immune when exposed to bites of Aedes aegypti mosquitoes of proved infectivity four other volunteers who served as controls were bitten by mosquitoes from the same lot and developed typically severe unmodified dengue The volunteers who had received the combination of dengue and yellow fever vaccine also developed neutralizing antibodies for the yellow fever virus Thus the material from extended passages could be used as a vaccine for production of immunity against dengue

Altered Taste in Dengue has previously been described To determine the significance of this symptom, Stephen R Elek[5] (M C, A U S) surveyed 154 dengue patients aged 18–38 in New Guinea Dengue resembles sandfly fever and may be confused with malaria Diagnosis in this series was established epidemiologically and by clinical and laboratory data Soldiers were stationed in a known endemic area harboring the dengue vector but not the sandfly fever vector Symptoms comprised sudden onset of fever and/or chills severe headache backache eyeache generalized muscle and joint pains anorexia rash leukopenia and a benign course Malaria was excluded in all cases by one or more smears

A bitter taste was described by 84 men (63 per cent) sour by 32 (24 per cent) sweet by 6 (5 per cent) and foul 'rotten egg slimy brown or rusty by 11 (8 per cent) Three patients had both bitter and sour tastes alternately The symptom occurred within a day of onset in 73 per cent of the men was referred to food and also persisted between meals It lasted an average of three days (one to nine)

Of 76 malaria patients (34 with Plasmodium vivax and 42 with Plasmodium falciparum) similarly studied 22 (29 per cent) had alteration of taste This was not an early symptom in malaria

Altered taste present early and often in dengue is an important symptom in differential diagnosis particularly in combat zones with limited facilities

(5) W Med 6 392 394 D embe 1944

intracerebral inoculation Although initial adaptation to the mouse is tedious and difficult, 16 consecutive passages were achieved in one series and further passages are in progress The virus propagated in mice produced dengue in human volunteers, but it was not pathogenic for cotton rats, guinea pigs hamsters or rabbits This limited host range may be used to differentiate it from two groups of viruses occasionally carried spontaneously by mice namely, the virus of lymphocytic choriomeningitis and the encephalomyelitis viruses isolated by Theiler

Sixteen volunteers were inoculated with various passages of the mouse adapted virus Skin lesions occurred at the site of intracutaneous injection, and six to nine days after inoculation systemic manifestations including fever marked maculopapular and petechial rash leukopenia and enlargement of certain lymph nodes appeared Immunity to infection with the regular dengue virus invariably followed Although it was evident from the beginning that the virus had undergone a change even as result of two serial passages in mice fairly severe types of experimental dengue infection were produced in some of the volunteers inoculated with the virus from the first six passages Tests with the seventh ninth and tenth passage material on nine volunteers indicated an extensive modification of the mouse adapted virus in its pathogenicity for human beings Intracutaneous or subcutaneous injection of 0 2 cc of a 5 per cent centrifuged brain and cord suspension either did not give rise to systemic symptoms or after an incubation period of 8–10 days produced reactions not exceeding in severity those following typhoid vaccination, i e fever with or without headache and malaise for 24 hours or less A marked and extensive maculopapular eruption and terminally petechiae on the feet and ankles were usually observed When this dose of mouse adapted dengue virus was given simultaneously or mixed with the regular U S Army dose of yellow fever vaccine the rash was reduced to a small number of faint macules

tract is present in the intestinal contents and in the blood is discharged in the feces and possibly also in the urine and can be transmitted by materials contaminated from an excretal source or by flies Further experimental work must be done to solve the problems of serum jaundice and its relation to epidemic jaundice and the problem of unrecognized carriers or latent cases of infection

Etiology of Epidemic Hepatitis W Siede and K Luz[7] believe the causative agent is a filtrable virus based on experiments in which 21 specimens of duodenal juice from patients with epidemic hepatitis and five specimens from normal controls were each inoculated into a series of eight fertile chicken eggs by Woodruf and Buddingh s chorio-allantois cultivation method In the eggs inoculated with the control specimens three series had no embryo deaths and two series had but one attempted passage from the dead embryos to other series was unsuccessful Among the eggs inoculated with specimens from patients with epidemic hepatitis seven series had *no embryo deaths* Four *series had many embryo* deaths but the causative agent could not be cultivated by passage Ten series had embryo deaths and the causative agent was passed successfully through an average of four series Occasionally virulence was maintained through eight passages Chick embryos died in three to nine days average period was five days

The authors conclude that epidemic hepatitis is contagious with a characteristic epidemiologic and clinical picture Cultivation of the virus depends on aspiration of the duodenum early in the disease and refrigeration of contents until inoculation which must be done within 14 days The virus may be preserved in embryonal tissue eight days It seemed hepatotropic the liver pulp of dead embryos being particularly effective in securing passage

Acute Infectious Hepatitis in the Mediterranean Theater Including Acute Hepatitis without Jaundice

(7) Kl W h ch 2 70 J 1943

HEPATITIS

Etiology of Infectious Hepatitis An editor[6] points out that the experiences in World War II permit the conclusion that infectious hepatitis is the result of in sanitary conditions is a specific infection introduced via the alimentary tract and is spread chiefly through human excreta a view which was also held after World War I A close association in incidence with dysentery has been noted and its prevalence in forward areas and base camps heavily infested with flies suggests transmission from feces by these vectors Kirk told of the hordes of flies at El Alamein which swarmed over everything and presumably conveyed the infection to men who were unable to protect their food mess tins etc

Failure to establish the exact cause of infectious hep atitis stems partially from the limitation of experimental work to human volunteers animals generally being non susceptible to the disease Voegt in Germany reported transmission of the infection by injection of serum and by oral administration of duodenal fluid and urine and Cameron in Palestine presented evidence of the presence of a specific agent in blood and serum Findlay and Martin produced jaundice by intranasal instillation of nasopharyngeal washings from men who developed hep atitis after inoculation against yellow fever The work of MacCallum and Bradley showed that frank jaundice could be produced only with subcutaneous injection of serum or by spraying feces into nose and pharynx

Havens Paul and van Rooyen report transmission ex periments which clearly establish the fact that an in fective agent is present in the feces whereas Findlay and Willcox carried out experiments in West Africa and found the virus or infective agent in both feces and urine in feces it was found in filtrable form

It may therefore be concluded that epidemic jaundice is a specific infection The causative agent probably a filtrable virus invades the body through the alimentary

(6) Lancet 1 213 214 F b 17 1945

therapy and because of its epidemiologic implications

Therapy begins with early and reasonably strict bed rest of adequate duration and a high protein diet this shortens the course of the disease and decreases the incidence of chronic hepatitis Disappearance of jaundice is not necessarily an indication of recovery In the acute stage nausea and vomiting may be controlled by maintaining a fluid intake of 3 000 cc daily either orally or by vein In severe case with low protein intake plasma or whole blood is given intravenously If hemorrhagic phenomena occur or if the plasma prothrombin level is low vitamin K should be given parenterally in doses of 2–4 mg Whole blood transfusions are the most reliable method of counteracting hemorrhage of serious nature For abdominal cramps or pain belladonna or atropine not morphine or barbiturates is given Bile salts are contraindicated The average patient with infectious hepatitis requires six to eight weeks for recovery 5–10 per cent are still not clinically well at the end of three months

Infectious Hepatitis in the Garrison of Malta K Damodaran and S J Hartfall[9] (R A M C) observed 450 patients admitted in 1941 1942 and part of 1943 Sporadic cases occurred during the year but the peak months were October to December with 65 per cent of the cases Incidence in waves every four weeks suggested a four week incubation period and a short interval of infectivity probably limited to the preicteric stage These characteristics point to a virus disease probably acquired by droplet infection

Four clinical types were seen (1) Gastro intestinal type (52 per cent) with insidious onset of malaise anorexia vomiting constipation and epigastric distress After three to five days urine turned black One to two days later conjunctivas became icteric (2) Febrile type (30 per cent) with rapid onset of chills pyrexia (100 F or higher) relative bradycardia frontal headache retro orbital pain and generalized muscular pains On

(9) B M J 87 590 Nov 1944

M Herbert Barker Richard B Capps and Frank W Allen[8] (M C A U S) after February, 1944 conducted an organized study of infectious hepatitis as it occurred in American troops in the Mediterranean theater of war A total of 1 172 unselected cases were examined and 431 were followed until discharge from the hospital Various control observations and special studies were made on several thousand men Furthermore the disease was observed in different areas of the theater, a factor of importance since early cases tended to predominate in the forward areas while chronic cases accumulated in the rear

Studies included the graduated exercise tolerance test sulfobromophthalein test acetone icterus index methylene blue urine test and the cephalin cholesterol flocculation test using standard routine methods Spread of disease in this area was probably chiefly by the enteric route The essential pathologic lesion was involvement of the parenchymal cells of the liver with inflammatory exudates in the periportal areas and usually with lymphadenopathy In the typical case there was a prodromal period of acute symptoms, without jaundice and without enlargement of the liver followed by an acute icteric stage with enlargement and tenderness of the liver Finally there was a convalescent stage with disappearance of symptoms and jaundice and return of the liver to normal size Sometimes recovery is so protracted that the condition can be termed a chronic hepatitis In some cases an acute stage was reached without the appearance of jaundice although all other symptoms were the same Careful study of about 100 cases of this type without jaundice showed that it was a mild nonicteric form of acute infectious hepatitis diagnosis in these cases was occasionally difficult in absence of an enlarged tender liver but the exercise test nearly always established the correct diagnosis The condition is important because of possibility of development of chronic hepatitis resulting from inadequate

(8) J A M A 1 8 927 1003 Aug 4 1945

with necrosis but no obstruction of bile ducts cystic duct or bile canaliculi obstructive manifestations resulted from swelling and compression of parenchymal cells The authors doubt the catarrhal pathogenesis of catarrhal jaundice recent pathologic reports confirm the theory of parenchymal involvement Clinically the disease is indistinguishable from infectious hepatitis

Infectious Hepatitis in Middle East Walter P Havens Jr[1] (M C A U S) observed this disease among 200 American troops in the Middle East and found the clinical picture similar to that described by British observers

The disease began with a clearly defined preicteric period of five days duration characterized by anorexia chilliness fever headache nausea vomiting upper abdominal discomfort and generalized aches and pains of acute onset This phase was terminated by decline of fever and appearance of dark urine which marked the onset of the icteric phase Anorexia nausea vomiting and epigastric distress were associated with hepatic enlargement and tenderness during the first 10 days of jaundice at the end of this period the icterus usually diminished and the signs and symptoms regressed Recovery was uneventful in almost every case Only three patients relapsed and no associated etiologic factor could be found Average duration of jaundice was 27 days patients over age 30 averaged 5 days more of icterus Patients who had received antisyphilitic therapy within three months before onset of the disease had jaundice for 12 days more than the average A few patients received sulfonamides which appeared to have no effect on the jaundice

The disease was present in all degrees of severity ranging from the mild case with subclinical jaundice in which icterus was detected only by urine and blood serum examinations to the severe case with deep jaundice prolonged over 83 days Eighty one per cent of

(1) J A M A 126 17 3 S pt 1944

the third or fourth day the temperature dropped, on the fifth or sixth the urine contained bile then jaundice developed and symptoms subsided The fever resembled influenza So called postinfluenzal jaundice may in reality be infective hepatitis (3) Icteric (ambulatory) type (10 per cent) with icteric conjunctivas and bradycardia but few symptoms The group comprised teetotalers those over 35 and the Maltese (4) Type without jaundice (hepatitis sine icterus), with typical onset and symptomatology, tender and enlarged liver, leukopenia and lymphocytosis but normal urine and van den Bergh reaction

Other symptoms and signs occasionally present included enlarged spleen distention of the right lateral thoracic vein pruritus conjunctival congestion resembling radiating streaks from the corneal margin, diarrhea erythematous rash herpes labialis fainting epistaxis ecchymosis petechiae and hematuria Prothrombin percentage tested in 18 patients varied from 35 to 100 depending on severity of the case

Complications which were rare included acute hepatic necrosis (icterus gravis) and subacute hepatic necrosis which occurred more frequently but was less often fatal Two patients had second attacks

Alcohol consumption (beer, whisky gin sherry or champagne) precipitated jaundice in persons incubating the disease increased the intensity during the course and produced relapses during convalescence

Arsenic and gold therapy increased the liability of infection The jaundice incidental to arsenical treatment of syphilis resembled infective hepatitis occurred more frequently when this disease was prevalent and in the 14 cases in which it occurred bore no relation to duration of treatment—all indicating intercurrent infection in a liver damaged by arsenic Neither arsenic nor gold should be administered for at least six months after infective hepatitis When relapse occurs the interval should be even greater

Postmortem examination revealed diffuse hepatitis

with necrosis but no obstruction of bile ducts cystic duct or bile canaliculi obstructive manifestations resulted from swelling and compression of parenchymal cells The authors doubt the catarrhal pathogenesis of catarrhal jaundice recent pathologic reports confirm the theory of parenchymal involvement Clinically the disease is indistinguishable from infectious hepatitis

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(1) J A M A 126 17 3 Sept 1944

patients had mild to moderately severe disease while 19 per cent had severe jaundice Blood counts coagulation and bleeding time and erythrocyte fragility tests were normal The serum icterus index as a measurement of icterus was found valuable both alone and in conjunction with the bromsulphalein dye retention test The percentage of dye retained in the blood was in direct proportion to the height of the icterus index. Blood Kahn tests were negative for all but one patient

Urinalysis gave the most important early clue to diagnosis and occurrence of biliuria cannot be stressed enough as an important diagnostic sign Albuminuria occurred in a significant number of patients

Duodenal drainage was performed on a large number of patients early in the course of jaundice and failed to shorten the disease

Pigment disappeared from the stools of many patients as the icterus approached its height and in the severely sick acholic stools were common

Methylene Blue Test in Infectious (Epidemic) Hepatitis Sydney S Gellis and Joseph Stokes Jr[1] (Univ of Pennsylvania) *report that the modified methylene* blue test for bilirubin in the urine used in a study of infectious hepatitis with jaundice proved valuable in early diagnosis of preicteric hepatitis in evaluating the course of the disease and in prediction of impending relapse

TECHNIC —Two drops of a 0 2 per cent aqueous solution of methylene blue chloride was added to 5 cc of a prebreakfast urine specimen. If a green color resulted more methylene blue was added drop by drop and the last drop required to convert the green color to blue was recorded Pipets which delivered 20 drops of the solution per cc were used.

Methylene blue chloride proved satisfactory since the dye content of different lots showed little variation in color The change from green to blue can be made easily when reading the result in natural light If more than 5 drops was required to produce the color change the urine was diluted with distilled water and methylene

(1) J A M A 1 8 78 783 July 14 1945

blue was again added drop by drop until the end point was reached, correction was then made for the dilution factor This was necessary because the addition of more than 5 drops of methylene blue resulted in a color of such intensity that the end point was difficult to determine

Methylene blue tests on prebreakfast urine specimens of 1 000 patients with diseases other than hepatitis gave the following results 74 per cent of specimens yielded a blue solution after addition of 2 drops of reagent 24 3 per cent required 3 drops and 1 7 per cent 4 drops to convert the resulting green color to blue Thus in this series no specimens yielded a green reaction after addition of 4 drops of reagent On the basis of these results a test of 5 drops or more was considered positive

Therapeutic Trial of Methionine in Infectious Hepatitis Clifford Wilson M R Pollock and A D Harris[3] report on 100 cases of *infectious hepatitis* Methionine was given in alternate cases All patients were men except three in the treated group and two in the control group Average duration of symptoms was 8 3 days most patients had been jaundiced for 1–2 days Daily doses of 5 Gm dl methionine were given from time of admission until the urine became bile free for five days This quantity was considered roughly equal to the average content of the normal diet The drug was given in the morning and evening 2 5 Gm at each time A fresh solution of the amino acid was made daily kept in the refrigerator and given ice cold flavored with orangeade Control subjects received orangeade alone Greasy foods were omitted from the diet and an extra pint of milk and one egg were given daily Comparison of the two groups was made by clinical and biochemical criteria Clinical criteria were duration of anorexia jaundice and liver enlargement after admission period in hospital and frequency of relapses or recrudescences Biochemical criteria were duration of biliuria interval between admission and return of serum bilirubin to 2

(3) B it M J 1 390 401 M 4 1945

mg per 100 cc maximal serum bilirubin, and hippuric acid synthesis after disappearance of bile from the urine as a test for recovery of liver function

Results indicated that most criteria had a slight bias in favor of the methionine treated group, but the differences were not statistically significant Mean duration of jaundice was 16 days in treated and 18 6 days in untreated patients Duration of liver enlargement and of liver tenderness was slightly longer in the control group Duration of hospital stay was 4 4 days shorter in the treated group and there were five relapses in the treated group as compared with nine in the controls Duration of anorexia was almost the same in the two groups Comparison of the biochemical criteria also showed only small differences in favor of the treated group The *hippuric acid test done at the end of treatment* showed no significantly different mean value in either group indeed the result was slightly favorable to the controls

The authors therefore conclude that oral administration of methionine as done in this series had no significant effect on the severity or duration of the disease nor does it prevent relapses

Treatment of Infectious Hepatitis with Methionine G Higgins J R P O Brien R A Peters Alice Stewart and L J Witts[4] (Oxford Univ) administered methionine to alternate patients in a series of 37 with infectious hepatitis All were put on a low fat, high protein diet supplemented with extra vitamins Estimation of the methionine content of the diet consumed daily was 2 5 Gm. Twice this amount was given additionally to the treated patients in the form of synthetic dl methionine This was made up in the proportions of 10 Gm to 283 ml water containing 2 8 ml concentrated hydrochloric acid, the solution therefore contained 1 Gm methionine in 1 fluidounce Throughout the day five 1 Gm doses were given either in milk or flavored with fruit juice Thus the treated patients received 7 5 Gm methionine

(4) Brit M J 1 401 40 Mar 4 1945

daily Detailed biochemical studies were made on all patients

Results showed that administration of methionine did not significantly affect the clinical course of the illness the anorexia or the average duration of biliuria or of bilirubinemia The prophylactic value of the drug has been established in animals in which liver damage has been produced by use of diets rich in fat by reduction of protein intake or by exposure to noxious substances However these conditions do not seem to apply to most patients with infectious hepatitis Reduction of protein intake is not an etiologic factor in the disease The possibility that methionine might hasten the repair of damaged liver cells is granted but the effect seems to be too slight to be of clinical significance

Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and with Infectious (Epidemic) Hepatitis John R Neefe Joseph Stokes Jr and John G Reinhold (Univ of Pennsylvania) report experiments to determine if the causative agent of homologous serum hepatitis is present in the feces of persons with this disease They therefore compared the effects of oral administration of feces from patients with homologous serum hepatitis with those of administration of feces from patients with infectious (epidemic) hepatitis The feces were obtained from volunteers with hepatitis induced by experimental inoculation with an icterogenic mumps convalescent plasma from patients with hepatitis contracted during a spontaneously occurring epidemic of infectious hepatitis and from volunteers in whom hepatitis developed after experimental ingestion of feces obtained from the patients with spontaneous hepatitis

All inoculated volunteers were presumed to be susceptible to the disease i e under age 30 had no previous history of hepatitis and gave no clinical or laboratory evidence of hepatic disease Pooled specimens of feces obtained from six patients during various stages of

( ) Am J M S 10 9 3 J ly 1945

homologous serum hepatitis were given orally to 19 volunteers None showed evidence of hepatitis during a four to six month period of observation This suggests that the causative agent either was not present in the feces or was not active when given by the gastro intestinal route Pooled *specimens of feces from patients* with epidemic hepatitis were given orally to 12 volunteers Hepatitis occurred within 25 days in six of these confirming the observation of others that the causative agent is present in the feces of patients with the active disease Finally pooled specimens of feces obtained from two volunteers during the preicteric and icteric stages of experimentally produced infectious hepatitis were given orally to seven volunteers The disease developed in one after 26 days indicating that the agent was present in feces obtained during the active disease Pooled specimens of feces obtained from the same two volunteers three weeks after disappearance of jaundice also were given orally to seven healthy volunteers None showed hepatitis during a four month period, suggesting that the agent was not present in the feces three weeks after disappearance of icterus

Transmission Experiments in Serum Jaundice and Infectious Hepatitis John R Paul W P Havens Jr A B Sabin and C B Philip[6] first carried out trans*mission experiments* with *serum jaundice in the* Middle East and later supplemented the work by experiments in the United States Twenty six persons were tested *The icterogenic agent used was originally derived from* a serum pool collected during a study of sandfly fever in Egypt Material from this inoculum (pool 1) produced sandfly fever in 9 of 10 inoculated volunteers after incubation of three to five days About 70 days after first inoculation and 60 days after the attack of sandfly fever was over jaundice developed in one of the group and suspicion was immediately aroused that there had also been an icterogenic agent in this pool Hepatitis developed later in 3 more of the 10 volunteers

(6) J A M A 1 8 911 91 July 28 1945

giving an incidence of 40 per cent and strengthening the suspicion of the presence of an icterogenic agent in the pool

Serum obtained from one of the subjects who had jaundice after inoculation for the sandfly fever study was tested by skin tests on eight persons The serum was withdrawn 34 days after first inoculation with material from pool 1 and 60 days before jaundice developed Thus the sample was obtained during the early part of a long incubation period preceding the attack of serum jaundice Jaundice developed in three of the eight persons after incubation periods ranging from 94 to 132 days in two others nonicteric illnesses developed during the 130 day period after the skin tests

In experiments repeated later in the United States with pool 1 serum jaundice was produced in three of five volunteers inoculated parenterally oral administration was seemingly ineffective Thus jaundice was produced parenterally 10 times in 23 individuals with different (first and second) passages of the icterogenic material, the incubation period was invariably long

The study on infectious hepatitis takes note of the fact that like that of serum jaundice the agent of infectious hepatitis has not been transmitted to laboratory animals despite numerous attempts Nevertheless experiments with healthy human subjects have established certain important facts When fecal material from patients with the naturally occurring disease was fed to human volunteers two of three contracted the disease in 20 and 22 days Serum obtained from these two patients in the preicteric phase was filtered heated and fed to five human volunteers producing infectious hepatitis in four with an incubation period of 23–34 days The same material simultaneously inoculated parenterally in the same amount produced infectious hepatitis in 6 of 11 volunteers with an incubation period of 20–21 days Recovery of some of the latter group of volunteers some months before from serum jaundice did not protect them against an attack of infectious hepatitis

Experimental work indicates that the agent or agents of serum jaundice and of infectious hepatitis are quite similar, clinical pictures of the two diseases are also similar both resembling catarrhal jaundice The agent or agents of both conditions are filtrable and relatively resistant to heat A main difference between the two is length of the incubation period which for infectious hepatitis lasts from 18 to 30 days and for serum jaundice from 60 to 120 days

Hepatitis after Yellow Fever Inoculation Immunology and Epidemiology G M Findlay N H Martin and J B Mitchell[7] state that like infectious hepatitis postinoculation jaundice is not highly infectious but some evidence suggests that contact infection may occur As previously demonstrated the icterogenic agent may be obtained from nasal washings The possible spread *from primary inoculated military personnel to nonvaccinated* contacts was shown in two cases Infectious hepatitis is not uncommon and about 5 per cent of adult European males have had one attack in childhood or adolescence Since second attacks are rare a considerable degree of immunity may be conferred Among 689 persons in whom icterus appeared after yellow fever inoculation only 4 gave a history of a previous attack of infectious hepatitis suggesting that jaundice developed in persons who had not been immunized by a previous attack of infectious hepatitis

A complement fixation test was developed with an antigen prepared from the liver of a patient who died of acute necrosis of the liver and a control antigen similarly prepared from the liver of a patient who died of heat stroke Five of six serums from patients with yellow fever inoculation hepatitis were positive with the hepatitis antigen and all were negative with the control antigen The sixth serum failed to show a positive fixation up to test level The serum of a volunteer in whom passage of postinoculation jaundice was produced via the intranasal route *also gave positive results with the*

(7) Lancet 2 365 370 Sept 16 1944

hepatitis antigen All control serums from random patients in a general hospital were negative except one which was positive up to test level

Numerous attempts to transmit the disease to animals by various routes have been unsuccessful Negative results in 22 volunteers inoculated by different routes with material from patients with well marked postinoculation jaundice are in striking contrast with the positive results previously obtained by intranasal instillation of nasal washings from patients in the preicteric period It may be concluded that the icterogenic agent either has disappeared from the blood or has been neutralized shortly after the appearance of icterus

The method of preparation of the yellow fever vaccine responsible for the present outbreak supports the assumption that the jaundice was caused not by the yellow fever virus but by something contained in the apparently normal human serum Occurrence of a similar type of jaundice after injection of serum plasma and possibly of whole blood indicates that human blood may sometimes contain an icterogenic agent All those who have at any time had infectious hepatitis should be discarded as donors of blood serum or plasma In preparation of yellow fever vaccine serum of any sort has now been abandoned

The authors conclude that the agents causing postinoculation jaundice and infectious hepatitis are identical or closely related the only difference between the two conditions is the longer incubation period in postinoculation jaundice

Hepatitis Following Blood or Plasma Transfusions Emanuel M Rappaport[8] reports on 31 soldiers who had jaundice and 2 who showed latent hepatitis without visible jaundice following transfusions of blood or plasma or both which were almost invariably necessitated by hemorrhage resulting from combat wounds Careful analysis strongly suggests that the parenteral blood products acted as a vehicle for the icterogenic agent

(8) J A M A 1 8 93 930 J ly 8 1945

Serial laboratory studies corroborated the clinical im pression *that the resultant hepatitis* was *primarily* par enchymatous Incubation period was 9–18 weeks, with an average of 12 6 weeks

Preicteric symptoms included anorexia malaise, lassi tude, headache, chilly sensations arthralgia myalgia epigastric pain and bloating with nausea and occasional vomiting or diarrhea all of them quite severe Fever was present in all Prodromal *symptoms lasted two to four* days before jaundice became evident and continued three *to five days thereafter* but *usually* disappeared rapidly even before icterus began to recede Clinically the con dition was indistinguishable from infectious or catar rhal jaundice spontaneously acquired or from cases of yellow fever inoculation jaundice Apart from icterus the most striking symptom was hepatomegaly without associated tenderness Despite this hepatomegaly in tense icterus and almost uniform laboratory evidence of derangement of the liver function, the clinical picture *did not reflect the severe hepatic damage in the acute* phase No death occurred despite the extreme initial cellular damage produced in the liver

To protect recipients of transfusions from doubtful sources quantitative bilirubin determinations should be performed routinely at monthly intervals from the third to the sixth month after transfusion This is of practical importance since hepatitis without icterus may result in as severe disabling conditions as hepatitis with jaun dice Unless the etiology is established at the outset its recognition at a later stage may be extremely difficult

Since persons with a *history of recent jaundice* are not accepted as volunteer donors at blood banks the icterogenic *agent may have been transmitted by subjects* in the preicteric phase of infectious hepatitis or by healthy carriers *Because of multiple transfusions ad* ministered at successive medical installations in the course of evacuation of military *personnel the problem* of tracing the contaminated plasma responsible for the complication is extremely complex *One way to begin*

tracing the source of contamination is by recording plasma lot numbers immediately after use This method is practicable with yellow fever and measles vaccine The prophylactic use of gamma globulin either by addition to pooled plasma or by intramuscular injection after transfusion should be tried

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INFLUENZA

Clinical Studies of Influenza Epidemic E Lee Shrader[9] studied an outbreak in two companies A and B of the A S T Unit at St Louis University in November 1943 The companies messed together and were quartered in six buildings separate from the rest of the unit They were divided into seven class groups Class schedules precluded intergroup mingling during classes Housing was by class groups or multiples of class groups The personnel had been selected from camps throughout the country and came from homes as widely distributed Inherent health was good However one to five cases of influenza had occurred each week beginning with that ending August 28 From October 31 to November 7 companies A and B were dispersed on furloughs

On November 9 a Company B man, returned from San Diego and on November 10 a Company A man returned from New York reported ill with influenza Neither had had known contact with any sickness On November 12 13 and 14 there were 32 (25 from Company A) 6 (5 from Company A) and 36 (14 from Company A) cases respectively Both companies were quarantined all activities suspended and medical inspections including the taking of temperatures instituted twice daily All men with fever or who felt ill were isolated or hospitalized On November 15 33 cases (7 from Company A) were discovered on medical inspection Following this case incidence declined the rate on successive days being 14 1 6 1 and 1

There was a total of 132 cases (25 9 per cent) in

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[9] L cet 64 413-417 D cemb 1944

Company A, 64 cases among 268 men (23 8 per cent), and in Company B 68 among 242 men (28 per cent) Incidence by buildings varied from 18 to 44 per cent, by class groups, from 7 5 to 49 1 per cent, indicating that the spread of infection was primarily by class groups secondarily influenced by building contacts No correlation existed between spread of the disease and proximity of the beds

The disease was characterized by sudden onset a four day fever with temperatures ranging from 99 to 104 F (usually 101–102 F) and occasional transient recurrence and vague symptoms consisting of malaise, chilliness mild generalized aching moderate prostration and rarely some abdominal discomfort Findings were meager—injected conjunctivas and flushed face—and disproportionate to the febrile reaction The white blood cell count was usually low but occasionally normal or elevated Early bed rest reduced the severity and duration of the attacks No complications occurred

There were also subclinical cases The patients had temperatures of 98 8 F or 99 F but felt well Some remained asymptomatic some developed a mild course and still others continued asymptomatic but became more febrile Such cases are important from the epidemiologic viewpoint as the disease is probably as infectious as that of the really ill yet the patients are not sick enough to seek attention voluntarily Control of such a highly infectious outbreak depends on early and thorough case finding inspections

Diagnosis of Influenza Virus Infections by Agglutination Inhibition Test *This test first described by* Hirst in 1941 has greatly simplified the technic of influenza virus studies It can be readily adapted to use in the serology laboratory of a hospital The virus suspension and immune serums used are quite stable at ice box temperature and can be supplied by a biological firm Human group O red blood cells can be used instead of chicken cells

Thomas W Farmer and George A Streeter[1] studied 14 nurses and medical students hospitalized during the epidemic of December, 1943 They presented similar clinical pictures Onset was sudden with fever chilliness and lethargy Coryza and sore throat were present in some Pain in the leg muscles backache and pain behind the eyes were common symptoms The maximum temperatures ranged from 101 to 105 F orally and the febrile period lasted two to four days No complications were noted In 10 of the 14 pairs of serums tested for influenza A infection there was a fourfold or greater increase in the in vitro level The average rise in agglutination inhibition titer was sixfold None of the 14 pairs of serums showed a significant rise to influenza B virus

From January to April 1944 the authors studied 76 pairs of serums from patients with a variety of infectious diseases, including 22 with sporadic respiratory infections occurring after the influenza epidemic period and some with pneumonia measles mumps scarlet fever meningitis and chickenpox The acute phase blood specimens were all drawn during the first week of illness and the convalescent ones two to six weeks after onset of the disease None of these pairs of serums showed a fourfold or greater rise in inhibition titer to influenza A or B viru

[Th s procedure should be of great value particularly in recognizing sporadic influenza —Ed.]

Studies in Human Immunization against Influenza Duration of Immunity Induced by Inactive Virus G K Hirst E R Rickard and W F Friedewald (Rockefeller Foundation) have administered formalin killed influenza virus concentrated from allantoic fluid to inmates of seven penal institutions in five widely separated states One cubic centimeter of vaccine containing the concentrate from 5 cc of PR8 and 5 cc of Lee or W S allantoic fluid was injected subcutaneously No immediate untoward reactions occurred A few subjects showed

(1) B n J h H pk H sp 75 46 59 J ly 1944
( ) J Exper Med 80 65 273 Oct ber 1944

a mild febrile response on the first day after inoculation and had slight chills and malaise of brief duration Slight redness and swelling at the injection site, with moderate sore arm for 24 hours was common

The mean antibody increase two weeks after vaccination was approximately sixfold against the strains Lee and PR8 and fourfold against the current strain NY 43, whether tested by agglutination inhibition or complement fixation Although the mean level dropped a year later the titers of PR8 and Lee antibodies were still about three times the prevaccination level and the NY-43 titers were twice the original by both methods of testing

The vaccinations were done in the last two months of 1942 and early in 1943, and no influenza epidemic was reported in any of the groups until the nation wide epidemic started in November 1943, when institutional epidemics were reported in all seven groups, concurrent with influenza in the general population The attack rate for the vaccinated group was consistently lower than that for the control group in each institution the over all reduction was 35 per cent

[This report would indicate that immunization against influenza will soon be on a practical basis—Ed]

Adjuvants in Immunization with Influenza Virus Vaccines Various agents tested experimentally by William F Friedewald[3] (Rockefeller Found) enhanced and prolonged the antigenic response

METHOD—Virus suspensions were prepared from a three day growth of PR8 strain of influenza A virus in allantoic fluid Concentrated suspensions were obtained by high speed centrifugation or absorption of virus by chicken red blood cells and subsequent elution in buffer solution.

Mice were vaccinated with 0.5 cc of the test mixtures injected subcutaneously Immunity was then determined by testing at intervals for resistance with graded amounts of PR8 infected allantoic fluid instilled intranasally On the tenth day surviving mice were killed. All mice were examined and classified according to lung consolidation as described by Horsfall

Antibody production was measured by agglutination inhibition and occasionally by neutralization and complement fixation tests on vaccinated ferrets and rabbits Standard ferret and

(3) J Exp r M d 80 477 491 Decembe 1944

rabbit serums from preceding bleedings were included in each test to correct for differences in titer

In experiment 1 vaccination of mice with PR8 virus allantoic fluid in combination with adjuvants killed tubercle bacilli suspended in paraffin oil and an absorption base falba (a mixture of beeswax paraffin oils and oxycholesterins extracted from lanolin) Four weeks after vaccination control mice (receiving virus in saline) were resistant to 100 M I D (minimal infectious doses) of virus whereas treated mice were resistant to about 1 000 000 M I D immunity was increased in control mice for 8 weeks in treated mice for 26 weeks

In experiment 2 PR8 virus allantoic fluid in combination with the killed tubercle bacilli in paraffin oil and falba as in experiment 1 and PR8 virus allantoic fluid concentrated by red cell absorption and elution with adjuvants and without were tested for antibody production in rabbits Control animals had their highest titers in 2 weeks with a fall to low level within 16 weeks Titer in treated rabbits was 10 times higher reaching maximum at 4–6 weeks and persisting 26 weeks (longest period tested) Complement fixation tests gave similar results

Control animals which received concentrated virus suspension showed titers slightly higher than those of the other controls but not nearly as high or enduring as those of animals which received adjuvants Similar titers were obtained following inoculation of both concentrated and nonconcentrated adjuvant mixtures

In experiment 3 the antibody response of ferrets resembled that of rabbits the treated ferrets showing titers 50 times higher than those of the controls

In experiment 4 substitution of the saprophytic acid fast Mycobacterium butyricum for the killed tubercle bacilli in a similar suspension induced greater antibody response Titers were 100 times higher than control titers at 12 weeks and remained high for 24 weeks (longest period tested) Results of complement fixation tests resembled those of agglutination tests but neu

tralization tests showed a five hundred fold difference Antibodies against normal allantoic fluid, which were not produced by virus saline were also induced in low titers

In experiment 5 use of Mycobacterium butyricum in sesame oil as an adjuvant produced less response than was produced in experiment 4 but the response was greater than that in the controls or in animals which received the virus plus sesame oil alone or sesame oil with typhoid bacilli Paraffin oil and falba were less effective when used alone as adjuvants than when combined with acid fast bacilli but were more effective than saline suspensions

After inoculation with the killed tubercle bacilli mixture a firm subcutaneous nodule, 0 5–1 cm in diameter, developed and persisted for several months Overlying skin became inflamed but rarely ulcerated On cross section the nodules consisted of inoculum surrounded by a thick tissue wall containing large mononuclear cells lymphocytes and polynuclear cells Nodules which appeared following inoculation of Mycobacterium butyricum were smaller and disappeared faster

Hyperimmunization induced by adjuvants is probably due to localization and maintenance of antigenic material by the reactive tissue wall, and consequent slow continuous adsorption of antigen from the mass Mononuclear cells enhance the response The adsorption base (falba) increases tissue reaction as well as stability of the water in oil emulsion

Unfortunately, the adjuvants cannot be used in human immunization because of the possibility of formation of miliary lesions in the lungs the hazards attending induced sensitivity to tubercle bacilli and the marked connective tissue irritation caused by paraffin oil Further investigation is needed to find other materials

Preparation and Properties of Influenza Virus Vaccines Concentrated and Purified by Differential Centrifugation W M Stanley[4] (Rockefeller Inst) reports

(4) J Exper Med 81 193 218 February 1945

results of tests on influenza virus vaccines containing from 1 to 10 mg virus materials per cc., concentrated and purified from infectious allantoic fluids by one or two cycles of differential centrifugation and inactivated by different treatments Suitable inactivation of the virus preparations with retention of full red cell agglutinating activity and immunizing potency in mice was achieved by treatment with minimal amounts of formaldehyde or ultraviolet light Treatment with phenol or chloroform did not cause adequate loss of virus activity Excessive amounts of formaldehyde or of ultraviolet light caused a loss in red cell agglutinating activity and in immunizing potency Freezing resulted in immediate loss of red cell agglutinating activity of the formalinized vaccine Storage of the vaccines in the frozen state was accompanied by gradual decrease in red cell agglutinating activity Drying of the vaccines from the frozen state also resulted in a loss of red cell agglutinating activity and in the case of the formalinized vaccine in a loss in immunizing potency There appeared to be at least a rough correlation between red cell agglutinating activity and immunizing potency These factors of a purified formalinized vaccine containing 2 mg virus material per cc were unchanged following two months of storage at 4 C but were measurably decreased following storage for two months at 18–25 C and at 37 C At equivalent dosages of virus material the immunizing potency of formalinized centrifugally purified virus of formalinized virus purified by the red cell elution method and of infectious allantoic fluid was not measurably different The immunizing potency of a formalinized polyvalent vaccine containing centrifugally purified Lee PR8 and Weiss influenza virus materials at concentrations of 5 2 5 and 2 5 mg per cc respectively was essentially the same as that of a similar vaccine prepared commercially In both cases the protection afforded against the Weiss strain appeared to be better than that against the Lee and PR8 strains

The bacterial contamination that frequently accom

panies operation on a large scale can be controlled by adding 1 part per 10 000 of formalin plus 1 part per 100 000 of phenyl mercuric nitrate to the allantoic fluid immediately after harvesting without affecting the quality of the vaccine

This procedure and use of virus materials which have been purified and concentrated by a single cycle of differential centrifugation by the Sharples centrifuge are suitable for production of influenza virus vaccines on a large scale By this means influenza vaccines possessing 20 or more times the immunizing potency of infectious allantoic fluid and 10 or more times the immunizing potency of the usual commercial vaccine prepared by the red cell elution method can be manufactured rapidly on a very large scale with considerable ease and efficiency

Influenzal Meningitis According to Arthur W Ide (M C A U S) Haemophilus influenzae has been given first to third place as a bacterial cause of meningitis in children and fourth place as a cause of meningitis for all ages The greatest mortality (90–100 per cent) has occurred in patients aged 2 months to 2 years Improved methods of early diagnosis and treatment are lowering this mortality remarkably although the organism and its virulence are the same Alexander has advocated immediate administration of sodium sulfadiazine by intravenous drip to establish a blood level of at least 10 mg per cent Large amounts of normal saline or Ringer s solution are given in the infusion to wash through the kidneys the toxic material released by the organism and found in the body fluids Antiserum is added to the infusion later and given slowly in amounts varying inversely with the level of spinal fluid sugar less antiserum is required because there is less specific soluble substance in the body fluids Slow intravenous administration is necessary to avoid the possible shocking effect of sudden union of antibody and antigen One hour and 24 hours after completion of serum therapy capsular

(5) Minnesota Med 7 816 819 Oct b 1944

swelling should be tested by adding a 1 10 dilution of *the patient s serum to a suspension of the organism in* the spinal fluid Further serum therapy is given only if capsular swelling is absent If there is no response to treatment in 48 hours anti influenzal serum should be given intrathecally

Ide presents the statistics on Haemophilus influenzae meningitis at Ancker Hospital St Paul for 1938 to 1943 The incidence of bacterial involvement for menin gitis of all ages was meningococcus 20 cases tubercle bacillus 16 pneumococcus 9 and Haemophilus influ enzae 9 Incidence in patients under 2 was Haemophilus influenzae 7 cases pneumococcus 4 meningococcus 3 and tubercle bacillus 1 Only two patients with in fluenzal meningitis recovered One girl 4 was treated with neoprontosil and repeated spinal drainage she recovered after six months hospitalization Another girl aged 14 months received sulfadiazine and anti Haemophilus influenzae type B rabbit serum she was discharged with nerve deafness as the only symptom *after 23 days hospitalization*

Neurologic Signs in Mice Following Intracerebral Inoculation of Influenza Viruses Gertrude Henle and Werner Henle[6] (Univ of Pennsylvania) state that when allantoic fluids containing active virus of human and porcine influenza are inoculated intracerebrally into mice marked hyperirritability appears in up to 100 per cent of the animals When suspended by their tails they exhibit marked tremor and clonic convulsions which may change suddenly into tonic convulsions Death occurs in a high percentage of animals Those that sur vive are markedly spastic for a few minutes and refrac tory to convulsions for a short time Depending on the concentration of virus in the inoculum most animals die within 24–72 hours with the described signs either spon taneously or while suspended However, death in convul sions may occur as early as 12 hours and as late as 8 days

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after injection The brain tissue shows definite changes of meningo-encephalitic nature

These cerebral signs may be prevented by neutralization of virus preparations with high titered immune serums derived from various species The agent as present in influenza A cultures is neutralized only by anti influenza A serum and not by anti influenza B or anti swine influenza serum while the reaction due to influenza B preparations is inhibited only by anti influenza B serum and not by the other serums The phenomenon *of cerebral signs has been observed so far only with* active influenza virus inactivation by ultraviolet irradiation heat or formalin rendered the preparations innocuous On the other hand when high concentrations of irradiated virus were injected simultaneously with active homologous or heterologous virus reduction in the incidence of convulsions was noted as compared with the incidence in controls inoculated with active virus alone

Neurologic signs caused by influenza virus have been previously reported by Stuart Harris and Francis and Moore who succeeded in adapting certain strains to mouse brain passage In their experiments infected chick brain tissue cultures or mouse lungs served as starting material the virus multiplied in the brain tissue neurologic signs developed only after 3–12 cerebral passages the incubation period varied from 3 to 11 days and only two strains (WS and Melbourne) could be established in this way In the present series mainly allantoic fluid preparations of influenza virus were used which caused neurologic signs on first passage to mouse brain usually within 24-72 hours the agent could not be passed from brain to brain in series and all strains of influenza tested (PR8, WS Weiss F 12 and F 99 strains of influenza A, the Lee strain of influenza B and a strain of swine influenza) gave positive results These apparent differences may be explained by assuming that influenza virus in sufficient concentration is toxic for brain tissue without showing *propagation in* the central nervous system

Visceral Leishmaniasis Joseph H Burchenal and Robert P Woods[7] report three cases which demonstrate certain factors not always found in the classic textbook case Thus the condition may be far more severe and progress much more rapidly than usually described or it may be so mild and localized that systemic symptoms do not appear Again the parasites may be so sparse in sternal marrow smears that intensive search is needed to find even a single organism In some cases it may be necessary to do a splenic puncture to establish correct diagnosis however sternal aspiration should always be tried first Early diagnosis and prompt treatment are vital to prevent development of granulocytopenia

The disease should be suspected in cases of unexplained fever in troops who have been residing in endemic areas even though it is relatively rare Differential diagnosis includes malaria enteric infection brucellosis tularemia bilharziasis trypanosomiasis miliary tuberculosis sub acute bacterial endocarditis and lymphoma Symptoms are long continued fever often with a double daily ele vation of temperature progressive splenomegaly followed by hepatomegaly loss of weight leukopenia with a white blood count sometimes as low as 1 000 and anemia which may progress to a hemoglobin content of 50 per cent Generalized lymphadenopathy has been noted

Mortality in untreated patients is about 90 per cent Results of treatment are good and in some series 94 per cent of permanent cures have been reported Potas sium antimony tartrate is still used when other less toxic drugs are not available It is given intravenously in 2 per cent solution every second day for 40 injections with an initial dose of 2 cc which is increased to 5 cc if there are no reactions The less toxic drugs are the pen tavalent antimony derivatives such as neostibosan neo stam and sodium antimony gluconate The form of kala azar seen in India is relatively susceptible to treatment with either pentavalent antimony or a diamidine prep-

[7] W Med 7 173 177 M h, 1945

aration diamidinostilbene The form seen in the Sudan is relatively refractory to the former and requires fairly large do es of the latter drug The authors have used sodium antimony gluconate intravenously in dosage of 6 cc daily for 10 injections and found this well tolerated In two patients somewhat refractory to this dosage 12 cc of the drug was given daily with good results and no reaction Another patient received a total dose of 282 cc for six weel s When diamidinostilbene is used symptoms such as mild flushing or even collapse apparently due to peripheral vasodilatation are avoided by simultaneous administration of a small dose of epinephrine hydrochloride Napier and his co workers obtained good results with this drug by giving an initial dose of 40 mg intravenously then successive daily doses of 75 90, 120 and 150 mg until a maximal daily dose of 1 5 mg per lb body weight was reached Maximal dosage should not be exceeded The usual course consists of 10–12 injections including the initial dose and may be repeated after an interval of one month

The criteria of cure are important because a second or third course of treatment may be needed Within two weeks of completion of treatment the temperature should return to normal and remain there the leukocyte count should show a distinct increase, the spleen should decrease in size and there should be gain in weight Ninety five per cent of relapses appear within four months Permanent cure seems established after six months without a relapse

Kala-Azar (Visceral Leishmaniasis) Simulating Splenic Anemia James S Sweeney Richard D Friedlander and Frank B Queen[8] (M C A U S) report a case of kala azar simulating splenic anemia in an Italian enlisted man 22 a prisoner of war who probably had contracted the disease in Sicily

Following a presumptive latent period of two years the disease appeared with manifestations resembling an acute surgical condition of the abdomen with fever gross distention of the abdomen with pronounced tenderness and splinting particularly

(8) J A M A 1 8 10 0 10 Aug 4 1945

on the entire left side and dulness on percussion in the left abdomen and flank An irregular febrile course followed tachy cardia developed and tentative diagnosis was peritonitis secondary to a possible splenic abscess Various measures including penicil lin produced improvement X ray films were then taken and those of the abdomen revealed a large soft t sue mass extending from the left diaphragm to just below the left iliac crest This was considered to be the spleen The patient s condition became sta tionary and he was transferred from the station hospital to a general hosp tal for further observation Further examinations and laboratory tests confirmed the fact that the mass was th spleen and diagnosis now became a problem including en larged spleen associated anemia cachexia albuminuria and low grade fever Possible diagnoses in luded the more likely causes of splenomegaly such as Bant s syndrome thrombosis of the splenic vein splenic infar tion leishmaniasis schistosomiasis chronic malaria Hodgkin s disease leukemia or primary neo plasm primary amyloidosis gumma or tuberculoma of the spleen Many laboratory tests and further x ray examinations were made but diagnosis still could not be made definitely Laparotomy was finally performed and the enlarged spleen was removed The postoperative ourse was stormy at first but recovery fol lowed.

Histopathologic studies of the spleen showed presence of Leish n an Donovan bodies which had not been found preoperatively in the numerous examinations of the irculating blood and bone marrow The patient was given a postoperative course of neo stibosan with apparent success since numerous blood smears for Leishman Donovan bodies made afterward were negat ve and the formol gel test which had been strongly positive at first became only faintly pos tive

The authors point out that kala azar must be consid ered when there are unexplained splenomegaly and as sociated signs and symptoms because of the recent im portation of prisoners of war to the United States and the return of American soldiers from countries where leishmaniasis is endemic

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MALAPIA

Newer Aspects of Malaria are discussed by M H Brodkey[9] (Creighton Univ) Recent reports from the Pacific area reveal that 50–65 per cent of military per sonnel have become infected with malaria as determined by positive blood smears Of these 35 per cent have be

(9) N b k M J 9 348 351 No embe 1944

nign tertian and 65 per cent malignant tertian malaria It is important to determine the type of malaria from the standpoint of both treatment and prognosis Malignant tertian malaria is the most dangerous type In natives in an endemic area it results in a high child mortality

In children in an endemic area acute malaria is manifested by lethargy and convulsions with or without chills in the chronic stage by anemia, apathy, debility and enlarged spleen The adult population in an endemic region is healthy although parasites are found in their blood stream In newcomers to these areas following the bite of a mosquito containing the sporozoite of Plasmodium falciparum 11–13 days elapse before symptoms appear Onset and exitus may be abrupt and dramatic—headache at noon and death by night The algid type is always dangerous The temperature curve shows fever for 16–36 hours with several irregular peaks before it falls A soldier under prophylaxis may harbor Plasmodium falciparum in his blood and show no symptoms However injury high altitude flying or chilling may change a dormant into an active case Whereas in benign tertian malaria the patient is allowed to have a few chills to establish a partial immunity and thus lessen the number of relapses malignant tertian malaria must be treated immediately

Prophylactic treatment does not prevent malaria The soldier in the field under prophylaxis actually has the parasites in his blood but his symptoms are suppressed A major army problem is getting the men to take the treatment The prophylactic dose of quinine is 10 gr daily that of atabrine 1½ gr daily for six days a week If suppressive treatment is discontinued most infected men will develop malaria within two to three weeks The army has considered staggering the discontinuation of suppressive treatment after the war so that the hospitals will not be overloaded with malarial recurrences

Specific treatment varies with the severity of the disease In uncomplicated malaria the patient is able to

retain oral medication Atabrine considered the best agent for this type of malaria is given in doses of 3 gr every six hours for five doses followed by 1½ gr three times a day for five days When quinine is used 15 gr is given three times a day for two days followed by 10 gr three times a day for five days Severe malaria is complicated with vomiting coma or other serious disorders In any case in which the parasite density is over 100 000 or 5 per cent of erythrocytes are parasitized or fever in a falciparum infection is over 103 F 10 gr quinine dihydrochloride in 200–300 cc saline is given slowly intravenously this is repeated in six to eight hours if necessary Oral medication is given as soon as the patient can swallow Atabrine is best given intramuscularly 3 gr into each buttock and repeated in six to eight hours Thiobismol and mapharsen have been used successfully in checking certain phases of the malarial cycle Routine use of plasmochin is not advocated because of its toxicity and questionable results

Diagnosis of Malaria in West Africa D G Ferriman[1] reports experience with over 2 000 cases of malaria almost exclusively malignant tertian in white personnel in West Africa Most patients had not previously been exposed to infection and their stay in West Africa was short Drug suppression and antimalarial discipline were in force and the infection rate was less than in other coastal areas Most patients were seen early and pernicious cases were uncommon Only nine had blackwater fever four cerebral malaria and one the choleraic type all of these recovered Chronic malaria was present in only six patients

Since malignant tertian malaria mimics many diseases and is a dangerous condition demanding early treatment a certain routine was set up to promote early diagnosis and early therapy Antimalarial therapy was begun on finding a positive blood slide Slides were taken on admission in all cases Experiments showed that in low fever cases slides taken beyond 48 hours were of no diag

(1) B t M J 1 3 310 M 10 194

nostic value Slides were taken night and morning for 48 hours in high fever cases even though treatment had been started since it was found that parasites still appeared in many of them Routine use of sternal puncture does not seem justified in West Africa Certain clinical findings aided in diagnosis Thus splenomegaly was strongly indicative of the condition, tenderness of the spleen was virtually pathognomonic and definite tenderness under the left costal margin in absence of a palpable spleen became of great diagnostic value The anomalous behavior of many patients with malaria superficially resembling other diseases was helpful Deterioration was of aid patients with the common nonmalarial diseases concerned in differential diagnosis (febrile catarrhs simple enteritis and dysentery) tended to recover fairly rapidly The time relation between constitutional and local symptoms was also of value In the usual nonmalarial illnesses onset might be with constitutional symptoms only but local ones soon followed which persisted after disappearance of the former In malaria constitutional symptoms often preceded local ones by *days and persisted after their disappearance* The typical tertian periodicity of fever and symptoms was helpful but unfortunately was not common Actual rigor was very uncommon and usually indicated blackwater fever The combination of the symptoms of two nonmalarial diseases such as coryza and diarrhea was felt to indicate malaria

Many cases were of a constitutional nature only with headache backache aching limbs dry cough vomiting fever, splenomegaly and herpes as symptoms Such cases should be considered malarial regardless of the findings on the slide until definite reasons appear to the contrary The group with constitutional symptoms only was the largest making up 83 25 per cent of the total Coryza or productive cough appeared in 9 25 per cent simple diarrhea in 4 5 per cent and dysentery in 0 75 per cent

From a study of blood slides it was concl[illegible] it

positive slides could be expected in most high fever cases of malaria and probably much less frequently in low fever cases Activation of latent malaria by nonmalarial illness was uncommon Cases of dysentery with negative slides and cases of simple diarrhea with low fever and negative slides were most unlikely to be caused by malaria

The term subclinical malaria was applied to a condition seen in ambulant personnel Chief complaints were recurrent headache backache aching limbs and malaise A sense of well being after treatment was a notable feature Splenomegaly occurred in about one third of cases and slight pyrexia was probably present The general condition was good and there was no anemia Blood slides were usually negative Response to antimalarial treatment was good

Treatment was given routinely for twice as long as it took the temperature to return to normal with a minimum of seven days Mepacrine was given from the beginning 0 1 Gm three times daily for a maximum of 10 days If longer courses were needed 10 gr quinine twice daily was substituted for mepacrine Quinine 10 gr three times daily was given in addition for the first two to three days for better initial control A five day course was given in cases in which spontaneous recovery was considered likely This was also used in hospital treatment of subclinical malaria Routine suppressive therapy consisted of 0 2 Gm mepacrine twice a week In the ambulant treatment of subclinical malaria 0 1 Gm mepacrine and 5 gr quinine were given daily for two weeks 0 1 Gm mepacrine was then given for six days a week either temporarily or permanently Results seem satisfactory with these routine courses

[This clinical study should be of great value to those who lack extensive experience with malaria —Ed]

Complement Fixation in Human Malaria Using an Antigen Prepared from the Chicken Parasite Plasmodium Gallinaceum Stuart W Lippincott Harry H Gordon Wm B Hesselbrock and Alexander Marble

(8) J Cl I v tigat n 24 36 371 M y 1945

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From a study of blood slides it was conclud[illegible]

tistics on the incidence of malaria in Iowa and the upper Mississippi basin. Incidence of malaria in the state rose from 24 cases in 1935 to 250 cases in the first six months of 1945 This striking increase is due largely to infection incurred outside the continental United States affecting men serving with the armed forces and persons in prisoner of war camps With so many malaria cases and with the well known tendency of the common tertian form to repeated relapse attending physicians laboratory technicians and health official should be especially alert for the possible appearance of sporadic cases or outbreaks of malaria in urban and rural communities

The Report of Malaria Survey along the Upper Mississippi River published under the auspices of the Board of State Health Commissioners Upper Mississippi River Basin reviews the work done subsequent to 1940 Five species of anopheline mosquitoes were collected and studied during the survey including Anopheles quadrimaculatus the chief vector for the spread of malaria The report urgently recommends that with the return of armed forces personnel from abroad personnel of laboratories in the region should include experienced technicians who are capable of determining the presence or absence of malarial parasites in blood films

[It is to be hoped that similar studies and commendations will be made in other localities if the malaria danger is to be averted —Ed.]

Large Initial Doses of Atabrine in Treatment of Benign Tertian Malaria James H Thompson[4] (M C A U S) reports on 100 cases of benign tertian malaria in American soldiers who contracted the disease in the Mediterranean area during the summer and had been treated and cured before being transferred to a non malarial zone All had received prophylaxis either quinine or atabrine in various dosages during part or all of their stay in the malarious area After transfer this prophylaxis was discontinued All but four who seemed to be true latent malaria patients had been

(4) J T p Med 47 61 64 D 1944-J 194

(Harmon Gen l Hosp Longview, Tex) studied the specificity and sensitivity of the complement fixation test with antigen from *Plasmodium gallinaceum* on 11 267 serums obtained from 1 000 normal healthy soldiers 95 soldiers with febrile illness other than malaria 481 men with syphilis and 505 soldiers with a history of malarial infection while in the South Pacific There were 434 recurrent attacks of malaria due to *Plasmodium vivax* in this last group during the observation period

Tests on single specimens of serum from the healthy soldiers showed 99 per cent to be negative Those on 475 serums from the soldiers with febrile diseases other than malaria showed 96 per cent to be negative Of 481 serums from syphilitic men 93 per cent were negative Of 9 411 serums from the 505 patients with a malarial history 67 per cent were negative 30 per cent positive and 3 per cent anticomplementary There was a maximum of 58 per cent positive tests on any one of five successive days during 234 recurrent attacks Complement fixation tests made before and after 300 recurrent attacks showed 33 per cent positive 5 days before the attacks 47 per cent positive 5 days after the attacks and 33 per cent positive 20 days after the attacks In the group with a history of malaria 121 patients were followed for six months at five day intervals 95 had recurrent attacks during this period the remaining 26 being free from attacks Tests on the serums of all these men exclusive of the period of attacks showed that only 36 per cent were positive

The complement fixation test using an antigen prepared from *Plasmodium gallinaceum* gives a group reaction of undetermined sensitivity for the serums of human beings infected with *Plasmodium vivax* it is, however, of no practical value in detecting latent malaria or indicating when a patient is cured

Malaria in Upper Mississippi Basin A report from the State Department of Health of Iowa[3] presents sta

(3) J Iowa St M Soc 35 331 Aug 1 1945

rapid recovery Toxic symptoms were more severe with the large initial dose, and this type of therapy should be reserved for patients whose relapse occurred after the initial 0 6 Gm dose routine and who did not have any toxic symptoms after the first cour e of atabrine The optimal time for giving either the 0 6 or the 1 Gm initial dose is 24 hours after the preceding chill in tertian fever

Possible Postwar Malaria Outbreaks in the United States I Snapper[5] points out that acute malaria out breaks may be favored by different conditions Thus introduction of a new active anopheline carrier has often proved to be the causative factor of a malaria epidemic The United States is however well protected against this contingency by the strict antimosquito quarantine which is organized at all airports where airplanes from malarious regions arrive Again changes of the physical characteristics of an area have often resulted in improved breeding facilities for mosquitoes and the ensuing increase of the malaria carrying an opheline population has been followed by an acute malaria outbreak Army and public health authorities of this country have by a nationwide campaign reduced the mosquito breeding areas to a minimum and careful legislation bars construction of reclamation projects which could lead to improved breeding facilities and thus to outbreaks of man made malaria The country is therefore well protected against this danger al o There remains the fact that a great number of return ing armed forces personnel may carry the sexual form of malaria plasmodia in their peripheral blood stream However experience all over the world indicates that if the other two main factors are controlled an increase in the number of malaria carriers does not cause acute malaria outbreaks Snapper therefore concludes that as long as public health measures against malaria continue the United States is not in danger of malaria epidemics caused by the return of Army or Navy personnel

(5) J Mt S i H p 1 708 715 M y Jun 1945

treated for clinical malaria Twenty four of the 100 had had relapses for which they had been treated before coming under Thompson's observation

Routine treatment in 78 cases consisted of an initial dose of 0 6 Gm, followed by 0 2 Gm after each meal for six doses, after which 0 1 Gm was given three times daily after meals for seven days Twenty two patients who served as controls were given 0 2 Gm every four hours for five doses followed by 0 1 Gm three times daily for five days Atabrine was always given after meals, if the initial dose was given before mealtime it was preceded by a pint of chocolate milk fruit juice or eggnog All atabrine was given in 0 1 Gm tablets orally Bed rest and physical therapy consisting of graded exercises were given Average hospitalization for 71 patients was 14 days longer hospitalization was usually caused by complications such as pneumonia anemia and surgical conditions When pneumonia and malaria occurred together sulfadiazine therapy was administered simultaneously A high calorie, high protein diet with additional vitamins and ferrous sulfate for anemia patients was given

The 0 6 Gm initial dose was quickly effective Of 36 patients 90 per cent had one or no chill after starting the course Toxic effects were never severe enough to interfere with the treatment the mild symptoms consisted of abdominal cramps diarrhea and vomiting Relapse rate during a two month period was only 4 per cent among those receiving the large initial dosage, contrasted with 23 per cent in the control group

It was assumed that the blood atabrine level had not been high enough in the patients who had relapses Since there were no facilities to determine the blood atabrine levels chemically these patients were retreated with an initial dose of 1 Gm atabrine followed by 0 2 Gm every four hours day and night for six doses then 0 1 Gm three times daily for a week Usually a patient had one severe chill about six hours after the initial dose, followed by no other chills whatsoever but by

continue the 0 1 Gm dosage three times a day for two to three weeks

The use of plasmochin to supplement atabrine or quinine has not proved of significant value and since the drug is dangerously toxic its use is discouraged

Practically the only indication for parenteral therapy in malaria is acute falciparum infection If the parasite count is above 50 000 per cu mm blood or if clinical symptoms are severe in the presence of a lower parasite count immediate parenteral treatment should be instituted. Such cases are not likely to be seen in troops discharged to civilian life but they have been seen in individuals returning from overseas by air who have become infected just before leaving the tropics and have developed their first symptoms after arrival in this country Onset of these cases is often insidious with coryza mild malaise or diarrhea and they have sometimes progressed rapidly to coma before recognition In such cases atabrine dihydrochloride in solution may be administered intramuscularly in simultaneous doses of 0 2 Gm in each buttock and the dose may be repeated at 8–12 hour intervals if the condition remains serious Oral treatment as outlined previously should be started as soon as possible to maintain a high blood level. Quinine dihydrochloride in solution is still available and may be preferred It is probably best to administer it intravenously in 0 5 Gm doses diluted with 200 cc normal saline solution glucose or plasma. The infusion must be given slowly and the blood pressure watched carefully since quinine may cause it to fall in which event epinephrine should be given

The problem in treatment of filariasis caused by Wuchereria bancrofti is primarily the lack of a drug which is effective against this worm. The adult worm inhabits the lymph vessels and lymph nodes and causes attacks of acute lymphatic obstruction and elephantiasis frequently of the scrotum and legs These symptoms often appear as early as three months after infection ...adult worms are still immature The attacks

Problems of Treatment of Tropical Diseases in Returning Military Personnel are discussed by Henry E Meleney[6] (New York Univ) The tropical diseases of *greatest concern in this regard are malaria and filariasis* Treatment of malaria in returned military personnel has two principal aspects treatment of relapses of vivax (tertian) malaria and recognition and treatment of early cases of falciparum (estivo autumnal) malaria

Relapses of vivax malaria occur mainly in troops who have taken atabrine as a suppressive measure in zones where malaria is hyperendemic and where other malaria control measures have been impossible Neither atabrine nor quinine is a true prophylactic against malaria It seems probable that many falciparum infections are entirely eliminated by suppressive treatment with atabrine, but most if not all of the persons infected with *vivax develop clinical malaria within a few weeks after* suppressive treatment is discontinued It is not known why vivax infections are so often not eliminated by the usual course of treatment

Atabrine like quinine affects mainly the asexual parasites which cause the symptoms of the disease The dosage originally advocated was 0 1 Gm three times a day for five to seven days It has been shown recently however, that although atabrine is quickly absorbed it is rapidly taken up by the fixed tissues and does not reach an effective concentration in blood plasma and red cells until the tissues are fairly well saturated Therefore it is now advocated that atabrine be given initially in doses of 0 2 Gm every six hours for five doses so as to raise the blood concentration to an effective level and that this be followed by 0 1 Gm three times a day for the succeeding six days Since atabrine is eliminated slowly *it is effective for several days after treatment is* stopped

If a relapse should occur after such a course it may be advisable in a subsequent relapse to continue the 0 2 Gm dosage every *six hours for six to eight doses or to*

(6) New York State J M 44 2105 2108 Oct 1 1944

ies three of the seven patients had been in West Africa less than a year

Rigor, considered typical of onset of blackwater fever occurred in only one case Three patients had an abrupt rise in pulse rate This rise from the characteristically slow pulse of malaria should indicate immediate examination of the urine for hemoglobin Great weakness and jaundice with anemia and cachexia and a typical color were present The liver was not palpable Convalescence was prolonged average hospital stay being 45 days The patients were invalided home with the recommendation that they never reside in a malarious country

Special care and caution must be used in giving blood transfusions in cases associated with severe anemia Cross grouping is always necessary to avoid severe reactions To prevent anuria 2 per cent sodium bicarbonate is administered by intravenous drip 1–2 pt being given fairly slowly i e one drop every two seconds Excretion of urine must be abundant and chloride loss must be replaced when anuria is present Treatment of established anuria consists of application of heat to the loins and an attempt at dry cupping The accompanying malaria is treated by a course of mepacrine starting with small doses e g, 0 1 Gm daily and gradually increasing to 0 3 Gm daily during convalescence The drug should probably be given even in the absence of parasites in the blood films otherwise malarial relapse may occur Anemia is treated by good food and large doses of iron

POLIOMYELITIS

Studies on Natural History of Poliomyelitis According to Albert B Sabin[8] (Rockefeller Inst) such studies have varied from speculative and unfounded hypotheses to too much reliance on limited experimental observations The latter pointed to droplet infection transmitted through the olfactory bulb to the central nervous system However Sabin found no lesion in 2 000 serial sections of olfactory bulbs taken at autopsy Other

(8) J Mt S n H p 11 185 206 N D 1944

are accompanied by fever and redness, swelling and pain of the part involved They last for a few days and usually recur at intervals of a few weeks They appear to be an allergic phenomenon due to the presence of the worm

Early diagnosis is mainly based on symptoms since the worms are immature and no microfilarias are found in the blood A few cases have been confirmed by finding young worms in lymph nodes removed for biopsy In a few individuals microfilarias may later be found in the blood without a previous history of lymphangitis

Most patients who are removed from the endemic *areas to avoid repeated infection never develop elephantiasis* A strong psychologic factor is involved in that infected patients have seen elephantiasis of the scrotum and legs in natives of the endemic areas and fear impotence and deformity They may be assured that impotence will not occur and that deformity is unlikely to develop

Blackwater Fever in West Africa E W Skipper and G L Haine[7] report 7 cases of blackwater fever among 2 355 cases of subtertian malaria in British and Allied military personnel No death occurred from either disease However the importance of this condition is illustrated by a case seen by the authors which developed *and became rapidly fatal in a man after his return to* the United Kingdom from the tropics

The disease is characterized by sudden intravascular hemolysis with liberation of oxyhemoglobin in the plasma From this methemoglobin and methemalbumin are formed which are excreted in the urine together with acid hematin these blood pigments impart the typical porter or stout color to the urine The condition is regarded as a complication of malaria especially the subtertian form *All seven patients had had previous* attacks of malaria, and four had not been treated adequately Blackwater fever develops in malarial persons who are not necessarily long time residents in the trop

(7) B M J 1 3 5327 Mar 10 1945

ing them human poliomyelitis stools Sabin fed a highly virulent monkey strain ('M V) to 5 cynomolgus monkeys and a recently isolated human strain (Per) to 15 None of the former but six of the latter developed poliomyelitis This suggests that infection by the oral route depends on the strain of virus as well as the host Of the six paralyzed monkeys four had no olfactory bulb lesions Virus was present in each motor cortex examined but was not found in the superior cervical sympathetic ganglions celiac plexus or spinal fluid (leukocyte count varied from 170 to 1 250 cells per cu mm spinal fluid) The pattern resembled an ascending progression through regional nerves with primary invasion of spinal cord or medulla The virus was localized in all levels of the alimentary tract except possibly the stomach and appeared most frequently in the mouth tongue pharynx and esophagus During the paralytic stage the virus was present also in the blood spleen kidney urinary bladder tonsils and occasionally various lymph nodes but not in the lungs

Infection of rhesus monkeys with recently isolated strains produced many nonparalytic cases Histopathologic studies of these explain transitory or nonexisting paralysis Partly damaged neurons may recover or destructive lesions may be so spotty as not to affect the major innervation of a given muscle

A working hypothesis of the behavior of poliomyelitis virus follows The virus enters through the mouth localizes and multiplies in the alimentary tract invades the spinal cord or medulla and here may or may not before establishing equilibrium with the host damage sufficient neurons enough to produce paralysis Equilibrium may be upset by severe exertion tonsillectomy adenoidectomy dental operations etc

Paul and Trask isolated poliomyelitis virus from flies caught close to rural privies used by patients Sabin selecting sanitary urban areas with good flush toilets trapped flies near garbage containers in the yards of patients who had been admitted to the hospital several

authors isolated the virus from stools of patients with poliomyelitis In a systematic search for the virus Sabin examined selected tissues taken at autopsy from bodies of patients who had died of the disease The virus was not consistently present in any one tissue It was frequently present in the motor cortex diencephalon mesencephalon medulla, pons and spinal cord and consistently absent in the olfactory bulbs anterior perforated substance (along the olfactory pathway) adjacent corpus striatum and anterior frontal and occipital regions It was not found in nasal mucosa salivary glands superior cervical sympathetic ganglions adrenals or cervical and mesenteric lymph nodes It was found once (primary bulbar poliomyelitis) in the sympathetic ganglions of the celiac plexus and in a pool of lungs liver spleen and kidney, as well as a mixture of axillary and inguinal lymph nodes from a patient in whom the *disease had been rapidly fatal Next to the central nerv*ous system the virus was found most often in the alimentary tract in the pharyngeal mucosa and tonsils in four of seven cases, in the wall of the ileum more often than in the wall of the descending colon and sigmoid but in the contents of the ileum less often than in the contents below suggesting a concentration from a higher focus

Patients were next studied nasal and expectorated material being collected during the first two weeks of paralysis for three days after which stools were obtained Nine of 23 stools proved positive but nasal and oral secretions were all negative Urine specimens were also negative

These findings indicate that the olfactory pathway need not be affected in humans that the nasal mucosa is not the site of virus multiplication and dissemination and that the walls of the alimentary tract are the source of virus in the stools

That oral infection may take place was demonstrated by Howe and Bodian (1940), who after severing the olfactory tracts of chimpanzees infected them by feed

litis epidemic since 1916 However even though this remarkable parallelism has occurred between sunspots and epidemics of poliomyelitis caution in interpretation and evaluation is needed As Ellsworth Huntington pointed out many terrestrial phenomena have a most exasperating way of fluctuating in harmony with sun spots for a considerable period and then suddenly showing a complete reversal of the old relationship

Further statistical examination of poliomyelitis as to age sex and geographic distribution shows that the greatest poliomyelitis epidemic in all history, that of 1916 was located chiefly in the urban areas of New Jersey New York, Massachusetts and nearby states and was most fatal at very young ages Lesser epidemics in later years had a very different geographic incidence, a larger proportion of male deaths and far fewer at the youngest ages

Persistence of Virus Excretion in Stools of Poliomyelitis Patients was studied by Dorothy M Horstmann Robert Ward and Joseph L Melnick[1] (Yale Univ) The stools of 46 paralytic and 15 nonparalytic patients were collected during the first or second week of the disease and at four to six week intervals thereafter Prepared material was inoculated intracerebrally and/or intraspinally into immature rhesus monkeys All but two monkeys were ultimately killed and a test was considered positive when microscopic lesions characteristic of poliomyelitis were seen in the spinal cord The two monkeys not killed exhibited typical paralytic poliomyelitis

This method revealed that 61 per cent of the patients excreted virus during the first two weeks of disease 50 per cent during the third and fourth weeks 27 per cent at the fifth and sixth weeks and 12 5 per cent at the seventh and eighth weeks Between the ninth and the twenty fourth week virus was detected in only 1 of 52 specimens that of a boy aged 8 in the twelfth week of paralytic disease In general no difference in virus

(1) J A M A 1 6 1061 106 D 1 1944

days or even weeks earlier Of 15 areas tested in Atlanta, Ga and Cleveland, 8 were positive for poliomyelitis virus as demonstrated in cynomolgus monkeys Rhesus monkeys gave negative findings The flies caught in Cleveland with meat bait were predominantly blow flies (especially Phaenicia sericata) those in Atlanta trapped with sugar and banana bait ordinary house flies (Musca domestica)

The high incidence of virus isolations from flies cannot be minimized Flies by contaminating food etc, may be important in the dissemination of virus during summer and autumn months and responsible for the seasonal outbreaks

Acute Anterior Poliomyelitis Walter G Bowerman[9] (New York City) presents a statistical survey of the influence of weather on the incidence of this disease In nearly every year the decline of poliomyelitis cases seems to coincide with the advent of the storms at and near the fall equinox

Careful evaluation of statistical evidence concerning the number of cases of poliomyelitis beginning with 1907 weather reports for the same years and sunspot numbers for the same period seems to permit the drawing of certain inferences (1) *dry warm summers seem* to be frequently associated with outbreaks of poliomyelitis in New York City (2) absence of rain seems more significant in this than changes in mean temperatures, (3) the case fatality rate (ratio of deaths to cases) of poliomyelitis in New York City has frequently been in accord with the cycle of sunspot numbers, thus with sunspot minimum there appeared decreases in rates Little is known concerning sunspots but certain facts are accepted Near sunspot maximums there is more ultraviolet light at least 30-50 per cent more than at a minimum and the weather tends to average out wetter and cooler Near a sunspot minimum the tendency is to have dry warm weather on the average as occurred in July and August 1944 the year of the worst poliomye

(9) Arch Pediat 62 57 77 February 1945

New Anatomic and Clinical Notes on Origin of Polio myelitis Carlos Preioni[3] states that poliomyelitis whether sporadic epidemic or endemic is preceded and accompanied by a similar epidemic among birds who thus furnish the reservoir for the virus In South America the epidemiologic route of poliomyelitis follows closely the route of river transportation of poultry i e along the La Plata with its great tributaries the Paraña and the Uruguay The intermediary vector between birds and human beings is probably Dismanisium avis An epidemic of poliomyelitis in early fall should be foreseen when in spring together with the pullulation of Dismanisium avis an epidemic is noted among fowl The ability of this vector to exist for months without food explains the prolonged latent period early fall is favorable to its development Two illustrative instances are cited

1 During an epidemic of poliomyelitis Preioni examined three children of a poultry raiser all of whom acquired the disease at the same time An outside source could therefore be excluded Investigation revealed that six months previously the farmer noted an epidemic of great proportion among his poultry some of the fowl died suddenly and others became paralyzed before death

2 Three paralyzed chickens taken from a coop in which many others had died were brought to a veterinarian Ten days later the younger of his two children developed *poliomyelitis with complete paraplegia of the legs*

Histologic examinations carried out on fowl from farms where children had poliomyelitis during the epidemics of 1941-42 and 1942 43 revealed the main changes localized in the anterior horns of the lower dorsal and lumbar segments of the spinal cord These changes were characterized by disappearance of nerve cells chromatolysis and presence of pyknotic sclerotic or polychromatic cells there were no inflammatory changes The spinal ganglions and the sciatic nerve showed interstitial lymphocytic infiltration *near the capsule or perineurium*

(3) S ma méd 51 1321 1331 J 9 1944

excretion existed between paralytic and nonparalytic cases or between younger and older patients No persistent carrier was demonstrated

Exposed Pulps of Teeth As Portal of Entry for Poliomyelitis Virus Myron S Aisenberg and Thomas C Grubb (Univ of Maryland) report on experiments and a field survey of the teeth of children with and without poliomyelitis during the epidemic of *1944* made to determine another portal of entry of the virus so far not definitely established

Five Macacus rhesus monkeys were inoculated with the poliomyelitis virus in the exposed pulps of anterior teeth Paralysis developed in one animal while the *nonparalytic disease developed in the others as indi*cated by histopathologic changes characteristic of the disease in the spinal cord and semilunar ganglions The teeth of 375 persons with poliomyelitis and 394 without the disease in the same age groups and geographic area were examined for evidence of pulpal exposure The patients with poliomyelitis showed an incidence of 65–70 per cent of pulpal exposures while the persons without the disease showed an incidence of 24–27 per cent This difference is statistically significant because it is from 3 3 to 5 6 times twice the standard error of difference

The authors recommend that a field study be con*ducted in which all exposed pulps of one group are* eliminated several months before the seasonal onset of poliomyelitis while the incidence of pulpal exposures in a *similar control group is recorded* but no dental treatment given Such an experiment properly carried out should indicate the importance of pulpal exposure as a portal of entry for the poliomyelitis virus If exposed pulps are found to be an important portal of entry, elimination of this portal by dental care before the poliomyelitis season should prevent many cases

[The four preceding articles *do much to clarify the epidemiology* of poliomyelitis —Ed.]

J A D A 3 5 6 Mar 194

until fed to chimpanzees There was much gross evidence of fly contamination on the material in the form of vomit and fecal spots The chimpanzees used had been protected from contact with poliomyelitis by all possible means The animals at no time showed any evidence of paralytic poliomyelitis after ingestion of the food and fly bait although temperatures of 101 F were noted Daily examination of specimens of stool from these chimpanzees was made before and after feeding the test materials The stools were prepared by ultracentrifugation and tested for virus by intracerebral inoculation in rhesus monkeys Control or prefeeding stool specimens gave negative tests for poliomyelitis virus indicating that the animals were not carriers originally Tests of seven separate stool pools in the postfeeding period gave positive results Typical poliomyelitis lesions were found in the cord and medulla of each of the infected test monkeys Passage of the strain of virus from two rhesus monkeys representing both chimpanzees produced characteristic poliomyelitis in two additional monkeys and was negative in mice guinea pigs and rabbits The evidence is therefore clear that poliomyelitis virus appeared in the stool of the chimpanzees in the period immediately after ingestion of the test material and also 20 days after the last feeding in one and 3–14 days in the other suggesting that the chimpanzees acquired subclinical infections or carrier states and that the virus multiplied in them

The only way the food and fly bait could have become contaminated with the virus of poliomyelitis was by the flies in the homes of the poliomyelitis patients

Prostigmine in Acute Anterior Poliomyelitis Malcolm S Eveleth and Allan J Ryan (New Haven Hosp) report on 12 patients treated early in the disease They all showed marked spasm of the back muscles and hamstrings and 10 had paresis of the legs All received Kenny treatment Prostigmine was first given subcutaneously 1 5 mg with 0 6 mg atropine sulfate to adults 1 125 mg with 0 4 mg atropine to older children and

(5) Y l J Bi l & M d 17 3 1 357 D mb 1944

Preioni assumes that the virus is transmitted from the reservoir by the vector to the skin of human beings in children mostly to the exposed legs where it produces local and general lymphangitis (lymphatic sepsis) This is the lymphotropic stage, clinically it is manifested by pain The perineural lymphatics convey the virus to the nervous system The spinal ganglions form the ultimate barrier Once this barrier is passed reflexes are abolished and paralysis supervenes In infants the virus enters through the face usually the only exposed part of the body, and produces facial paralysis In adolescents in large cities the exposed face neck and arms form the port of entry accordingly they develop the more severe types of poliomyelitis the upper spinal bulbar and meningeal Here the vast hordes of birds swarming on terraces church facades etc furnish the reservoirs for the virus

Because the process is mainly degenerative Preioni considers the term poliomyelosis more appropriate than poliomyelitis

[It is difficult to comment on this report except to say that no similar observations have been made in this country—Ed]

Poliomyelitis Virus in Fly Contaminated Food Collected at an Epidemic Robert Ward, Joseph L Melnick and Dorothy M Horstmann[4] (Yale Univ) report the detection of poliomyelitis virus in food exposed to flies during an epidemic in the summer of 1944

Fly bait and food were exposed at 12 homes of poliomyelitis patients and food alone at 8 homes in a week after onset of illness The food consisting of sliced bananas sprinkled with sugar and water was purchased locally, prepared at the site of exposure and exposed on plates usually in the kitchen and on the back porch Families were warned not to touch the plates The fly bait, composed also of bananas and sugar and liver or fish also obtained locally with water to prevent desiccation was placed in a fly trap in the yard or on the back porch All material was exposed for 24–48 hours frozen on dry ice, transported to the laboratory and held frozen

(4) Sc e 101 491 493 May 11 1945

in most instances and there were no side effects Electro cardiograms taken before and after administration of prostigmine showed no changes induced by the drug

[The two preceding reports are contradictory It is unlikely that prostigmine will provide an important improvement in the treatment of poliomyelitis —Ed]

Significance of Muscle Spasm in Acute Stage of Infantile Paralysis Based on Action Current Records R Plato Schwartz Harry D Bouman and Wilbur K Smith[7] (Univ of Rochester) point out that an objective analysis of various concepts of the disease shows that there is common agreement on one point namely that neuromuscular dysfunction is the cause of disabilities following the disease Therefore to lower the incidence of disabilities more effective methods for preventing impairment of muscle function must be found based on better understanding of the neuromuscular mechanism in the acute stage The authors investigated the characteristics in the behavior of the neuromuscular mechanism primarily as related to the acute state of the disease for comparison with the recorded characteristics of normal persons and the records of patients with other established neuromuscular disabilities A total of 50 individuals were studied including 9 normal subjects 6 patients with spastic paralysis 23 with infantile paralysis and 12 with miscellaneous conditions

Results of the investigation permit the conclusion that the spine sign in infantile paralysis (spasm in muscles of the neck and back) is a gross manifestation of the lesser degree of spasm recorded in muscles of normal and subnormal strength Certain functional abnormalities other than muscle weakness observed in the lower reflex arc in association with spasm could be most readily explained in terms of dysfunction at or proximal to the dendrites or cell body of the lower motor neuron This dysfunction resulted in a partial isolation of the lower motor neuron from the inhibition normally induced by other levels through long and short neural path ways The degree of lower reflex arc isolation thus estab

(7) J A M A 1 6 695 70 N 11 1944

0 5 mg and no atropine to younger children It was then *administered orally for 28 days in maximal toler* ated doses the average adult dose being 45 mg and 0 6 mg atropine three times a day Range of passive motion was measured before the initial injection, after one hour (during which Kenny treatment had been omitted) and at the end of the four week period

Patients experienced fascicular muscle twitching after *the injection and within a week subjective increase in* strength and freedom of movement On testing range of passive motion was considerably extended after the in jected dose However, at the end of the four weeks there was little improvement beyond that naturally expected

Use of Prostigmine and Modified Kenny Technic in Treatment of Poliomyelitis George J Boines[6] (Wil *mington Del) presents a report on 21 patients with* acute subacute and chronic poliomyelitis All received *treatment with the Kenny technic a modification thereof* and/or prostigmine The modification consisted of elimi nation of hot packs and substitution of prostigmine usually orally but occasionally also parenterally No change was made in the usual muscle re-education meth ods or in the passive joint movement procedure In ad dition the patients were given general supportive medi *cation to prevent anemia and anorexia (iron and* thiamine) and mild sedation

The results were highly encouraging Boines urges ex tension of this method of treatment especially in chronic cases He further contends that 75 per cent of patients with poliomyelitis can be adequately cared for at home

The parasympathicomimetic action of prostigmine does not fully explain its effectiveness in relieving muscle spasm in poliomyelitis The drug apparently finds its way *into the spinal cord* where it exerts a direct action, re sulting in a decreased tone of the muscles and reflexes Prostigmine is an *effective substitute for the burden* some hot packs which heretofore have been one of main stays of the Kenny method. *The drug was well tolerated*

(6) J Pediat 25 414-438 November 1944

distinct protective effects were obtained in rhesus monkeys which had received murine virus (animal passage or tissue culture virus) up to 48 hours after intracerebral infection with simian poliomyelitis virus Theiler s virus of spontaneous mouse encephalomyelitis when tested in mixture with simian poliomyelitis virus gave some evidence of irregular and low grade interference interference could not be shown conclusively in experiments to prevent poliomyelitic infection or to modify its effects

The factors which govern interference between murine and simian strains of poliomyelitis virus may prove to be fairly typical of viral interference in general Three factors are important (1) The phenomenon is quantitative in that definite proportions obtain between the opposing agents (2) Effective interference requires inordinately large amounts of the interfering virus far exceeding the amount required for specific immunization (3) Protection is considerably enhanced by continued administration of the interfering agent These factors suggest strongly that the interference reaction is chemical rather than biologic in nature Actually the entire process closely resembles the phenomenon of chemotherapeutic interference first described by Browning and Gulbransen In this a given trypanocidal agent when present in subeffective amounts in an infected animal will nullify the curative action of another trypanocidal agent given later Just as this chemotherapeutic interference can be elicited only at certain intervals and with certain amounts of the competing substances so is viral interference conditioned by dosage and time of administration of the interfering viruses

lished and the degree of viability remaining in the lower motor neurons therefore determined the amount of muscle spasm in each instance Without involvement of levels proximal to the lower motor neuron there would be no spasm but the muscle could be either weak or normal, depending on the number of normal motor neurons innervating the muscle It all motor neurons failed to be stimulated by the stretch reflex there would be no reaction to the stretch reflex even though relations proximal to the dendrites were normal Spasticity and weakening are two separate phenomena each dependent on specific disturbances of functions of the anterior horn cells There was every indication that spasm ran its course like other clinical manifestations of the condition The relationship between muscle tenderness and muscle spasm could not be clarified differentiation must still be made between pain and hyperesthesia from discomfort due to muscle soreness *Muscle spasm does not initiate the development of muscle weakness* nor was there any correlation between the degree of spasm and the incidence of muscle weakness or paralysis

Studies in Rodent Poliomyelitis Claus W Jungeblut[8] (Columbia Univ) reports further observations on interference between murine and simian strains of poliomyelitis virus *Attempts to separate by process of physical* segregation i e by ultrafiltration ultracentrifugation or dialysis from live SK murine poliomyelitis virus a nonpathogenic agent capable of interfering with simian poliomyelitis virus were unsuccessful It was also impossible to convert live SK murine virus into a nonpathogenic interfering agent by processes of chemical inactivation *i e by phenolization or formalinization* Preparations of SK murine virus which had been markedly attenuated by ultraviolet irradiation gave evidence of having retained some interfering power in rhesus monkeys MM murine poliomyelitis virus interfered both in mixture tests and by peripheral administration, with two simian strains With adequate amounts

(8) J Exper Med 81 275 94 March 1945

endemic typhus showed evidence of infection in a high percentage of the rats while the Weil Felix test was positive in much lower percentages The complement fixation test furnished evidence of rickettsial infection earlier than the Weil Felix test in 23 9 per cent of human serums From an epidemiologic standpoint the complement fixation test is superior to the Weil Felix test because a positive complement reaction persists longer both in humans and in wild rats than does a positive Weil Felix reaction Laboratories should use the complement fixation test as routine procedure in diagnosis of rickettsial disease when antigens are more readily available

Serologic Diagnosis of Endemic Typhus Samuel R Damon and Mary B Johnson[1] (Montgomery Ala) report on use of specially prepared rickettsial suspensions and commercial typhus vaccines as antigens in the complement fixation test The specially prepared antigens made from the endemic type virus were furnished by the National Institute of Health and Sharp & Dohme the latter also furnished a similar antigen of the epidemic type The vaccines were all prepared from the epidemic type virus by Lederle Laboratories Inc Parke Davis & Co and Eli Lilly and Co The standard serum used in titrating the antigens and vaccines was from guinea pigs recovered from infections with endemic typhus or from humans with active cases of the disease

TECHNIC —The clas ic hemolytic syst m of sheep cell gu n a p g complement and rabbit ant heep ell amb ceptor was u e l In determining the antigenic titer of the spe ally prepared rick tts al uspen ons or the va nes dilut on were first made from 1 4 to 1 1 8 by adding 0 1 c antig n t 0 5 c aline in th first tube and transferring 0 c of this dilution to the next tube wh h al eady conta ned 0 ? c alin This was repeated through the rema ning tubes of the seri s 0 cc be ng discarded f om the final tube To all tubes 0 cc standa d serum (diluted 1 8) was then added follo ved by 0 cc complem nt (? units) The tubes were next n ubate l ne hour at C after wh ch 0 4 cc sensitized sheep ells was add d The sensiti ed sheep cell suspens on was made by combining equal amounts of a ? p r cent sheep cell suspens on and rabb t ant sheep c ll ambo eptor wh h had been titrated to contain ? units in 0 cc The

(1) J L b & Cl M 1 30 23 36 M h 1945

Applications of Complement Fixation Test in Study of Rickettsial Diseases Ida A Bengtson[9] (Nat l Inst of Health Bethesda Md) points out that the complement fixation test is rapid comparatively simple and more specific than immunity tests in animals or the Weil Felix test The test was used for diagnosis of rickettsial disease in the following manner

TECHNIC —Twofold dilutions of inactivated serum in 0.2 ml amounts are used Two tenth ml of the antigen suitably diluted and 2 full units of complement contained in 0.2 ml are added After one hour s fixation in the 37 C water bath 0 4 ml of 2 per cent sheep red cells sensitized with 2 units of hemolysin is added and incubation continued for another hour at 37 C The test material is then stored at refrigerator temperature overnight and the results are read the next morning

Of approximately 1 000 serums tested for both Rocky Mountain spotted fever and endemic typhus 330 were positive by the complement fixation test for one or the other of the two diseases The titers of these serums ranged from 1 4 to 1 8 192 In most tests there was complete specificity without cross fixation Results also indicated that the test was more specific for Rocky Mountain spotted fever than for endemic typhus

Experiments with the Weil Felix test showed that the complement fixation test and the Weil Felix test supplement each other In most cases good agreement was obtained with both tests when used for diagnosis Although titers were not comparable they were significant If a high Weil Felix titer is obtained in a case with a low complement fixation titer a later specimen should be tested or the same specimen should be retested to render the test more sensitive Proteus infection should also be considered A high complement fixation titer with a low Weil Felix titer is considered evidence of rickettsial infection without further testing

In tests on serums from wild rats trapped in endemic typhus areas positive complement fixation reactions for

(9) Am. J Pub Health 3 01 07 July 1945

of agglutination tests with various serums from man and animals infected with or vaccinated against typhus cross agglutinations observed and serum absorption experiments Results of the tests showed that the rickettsial slide agglutination test using a concentrated antigen is a useful diagnostic aid in studies on typhus in human serums and in study of agglutinin development in man and animals following infection or vaccination The test is particularly useful in mild cases of human typhus in which diagnosis is often difficult and the isolation of typhus rickettsiae from the blood is a lengthy procedure which may give negative results The agglutination test needing only one reagent is simple and rapid and differentiates strains of the infection from each other and from spotted fever The following method was used in these experiments

TECHNIC —Glass slides with 1 depressions were used The serum to be tested was set up in tubes in doubling dilutions and one drop of each dilution was transferred to the slide with a capillary pipette An equal volume of antigen was added with a pipette of the same bore The slides were then rotated by hand for thorough mixing and placed on moist paper in Petri dishes which were left in the incubator at 40 C for five hours They were then placed in the refrigerator overnight after which a final reading was made with the low power objective of an ordinary microscope Actually with serums having a titer of 1 80 or over agglutination in the lower dilutions was visible to the naked eye after incubation for 30–60 minutes and in much less time if the slide was rotated for 2 minutes

Positive and negative serum controls were included in each test in the study In absence of agglutination there is a perfectly smooth distribution of the antigen easily distinguished from even a 1 plus agglutination reading Any degree of agglutination is significant since normal serums give no trace of agglutination at all Complete agglutination where the entire field is covered by large clumps was considered a 4 plus reading smaller clumps constituting 3 plus and still smaller 2 plus readings

Chemotherapeutic Studies in Rickettsial and Virus Diseases Henry Pinkerton[3] (St Louis Univ) points

(3) South M J 38 371 373 Jun 1945

tubes were then reincubated for one hour, stored in the refrigerator overnight and read the next morning Amount of fixation was estimated as 4 plus (complete) 3 plus 2 plus, 1 plus plus or minus (trace) and 0 (none) The titer was recorded as the highest dilution showing 3 plus or 4 plus fixation Controls were et up with each titration.

Results obtained in titration of the rickettsial antigens when the tests were run at 37 C with one hour for fixation showed that all of this specially prepared antigen material was suitable for use in complement fixation tests When freshly made, it could be used in dilution of 1 16 or 1 32 There was some loss in antigenicity with time although the suspensions were still useful four to eight months after being titrated initially

A similar investigation of the commercially prepared typhus vaccines showed that those made by two of the manufacturers and representing 12 different lots were *satisfactory for use as antigens in the complement fixation tests* Not all the vaccines could be used as antigens in diagnostic tests in the same dilutions however some were good only when diluted 1 2 and others could be diluted as much as 1 4 The product of one company was entirely unsatisfactory as its vaccine was not capable of fixing complement in any dilution in which it was not anticomplementary The keeping qualities of the useful vaccines were good there was apparent loss of antigenicity in only one instance, evidenced by a drop in the dilution which could be made when using it as an antigen

The specially prepared suspensions of rickettsias have the advantage over the commercial vaccines in that higher antigenic titers were obtained This may be due to (1) the greater concentration of the suspensions, (2) the fact that they were prepared from endemic virus and (3) the use of endemic virus antiserum in carrying out the antigenic titrations

[Such diagnostic procedures should be of great value in rickettsial *diseases* the organisms of which are difficult to grow —Ed.]

Studies on Rickettsial Agglutination in Typhus Florence K Fitzpatrick (Glenolden, Pa) reports results

(9) J Lab & Cl n Med. 30 577 585 July 1945

Therapeutic Effect of Para Aminobenzoic Acid in Louse Borne Typhus Fever Andrew Yeomans (M C USNR), J C Snyder E S Murray C J D Zarafonetis and R S Ecke[4] (M C A U S) treated 20 patients with louse borne typhus at Cairo Fever Hospital with para aminobenzoic acid Their clinical course was compared with that of 44 untreated typhus patients The drug was administered orally The initial dose varied from 4 to 8 Gm in most cases followed by 2 Gm every two hours Adjustments in dosage were made in relation to fluid intake and urinary output The blood concentration of para aminobenzoic acid was kept at 10–20 mg per cent Treatment was continued until the patient s rectal temperature was 99 5 F or less for 24 hours The average amount of para aminobenzoic acid for each patient was 127 Gm To lessen gastric irritation sufficient sodium bicarbonate was given to neutralize the para aminobenzoic acid The usual amount was 2 Gm powdered para aminobenzoic acid with 25 cc sodium bicarbonate solution There were no unfavorable effects on the *blood cells* or *hemoglobin* except for a tendency to a low white blood cell count There were no renal complications attributable to para aminobenzoic acid therapy On the contrary the low incidence of nitrogen retention in the treated patients suggested that the drug may prevent renal damage in typhus If a patient is too weak or stuporous to swallow the drug should not be administered orally because of danger that severe tracheitis may be the result of its aspiration

The experience through two seasons of typhus epidemic in Cairo Fever Hospital has shown a very low incidence of mild cases in the untreated group Only one such case was encountered whereas fatal cases constituted 18 per cent of the total By contrast there were 11 mild cases when para aminobenzoic acid was given before the end of the seventh day of illness to 17 of the 20 patients treated None of the 17 died The length of

(4) J A M A 1 6 349 356 O t 1944

out that diseases of a rickettsial and of a viral nature with few exceptions have proved resistant to both sulfonamide and penicillin therapy This resistance is undoubtedly due to the fact that viruses and rickettsias grow inside the body cells and are partially or completely dependent on the enzyme systems of these cells Because of their intracellular location they may be protected mechanically from chemotherapeutic agents or may be invulnerable because of the complex interrelationship with the intracellular enzyme systems

Experimental work with typhus fever in guinea pigs showed the sulfonamides to be not only therapeutically ineffective but even detrimental Penicillin seemed more effective inhibiting the growth in yolk sacs of fertile eggs If given in large doses starting within 48 hours after injection of rickettsias penicillin had a strongly *positive chemotherapeutic effect in typhus infected mice* When para aminobenzoic acid was added to increase the effectiveness of penicillin it was found that the acid by itself inhibited rickettsial growth in the yolk sac so effectively that further experiments with penicillin were dropped and attention was concentrated on the acid Addition of the acid to the diet of typhus infected mice prevented the illness completely

It is known that para aminobenzoic acid neutralizes the bacteriostatic action of the sulfonamides By itself the acid is not bacteriostatic unless present in very high concentration Rickettsias exposed directly to para aminobenzoic acid even in concentrations as high as 1 3 000 are not killed Probably the acid exerts its effect by altering the metabolism of the cells so that their cytoplasm becomes a less favorable medium for rickettsial growth

Pinkerton emphasizes the fact that the work is still in experimental stages and that the toxic effects of the acid have not been completely studied The acid may be effective in other rickettsial diseases and in certain viral diseases but further knowledge of the individual intracellular enzyme systems is required to *discover methods* for selectively stimulating or inhibiting action of each

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(4) J A M A 1 6 349 3 Oct 1944

time between onset of illness and discharge averaged 32 days for the untreated group and 21 days for the treated patients Para aminobenzoic acid lessened the severity of typhus The treated patients developed few of the troublesome complications which usually occur such as coma stupor prostration fall in blood pressure urinary retention oliguria nitrogen retention and incontinence of urine and feces High blood levels (up to 49 mg per cent) of para aminobenzoic acid produced minimal constitutional effects

If organisms susceptible to action of penicillin are encountered in secondary bacterial infections in typhus, use of penicillin to supplement para aminobenzoic acid therapy is advised rather than sulfonamides The effect of sulfonamides on experimental typhus seems to be deleterious whereas that of penicillin is beneficial Para aminobenzoic acid inhibits the action of sulfonamides on bacteria in vitro

The authors advance the hypothesis that para amino benzoic acid inhibits multiplication of rickettsias inside the cells thereby permitting the immunity mechanisms of the body to dispose of them It is also possible that its action is directed against the toxic substances released by the rickettsia

Scrub Typhus An Unusual Case Simulating Mumps is reported by H S Patterson (A A M C)

Man 34 complained of dizziness severe frontal headache and swelling in the right parotid region There was also a stye-like lesion of the right upper eyelid A provisional diagnosis of mumps was made

On the second day the redness and swelling of the eyelid were more obvious and a small scabbed lesion was noted at the midpoint of the lid margin The fourth day there appeared a pink macular rash on the trunk and bilateral axillary adenitis he complained of increasing severe frontal headache and back ache The temperature which had varied between 99 4 and 101 4 F rose steeply to 103 4 F The right parotid swelling was still obvious but no swelling of the left parotid or other salivary glands had occurred In view of the rash adenitis type of temperature curve and severe headache and backache the provisional diagnosis was changed to scrub typhus This was confirmed by

(5) M J Australia 2 138 Aug 5 1944

the Weil Felix agglutination test which was positive in a titer of 1 1,280 Cough appeared on the fifth day and high pitched rhonchi and scattered crepitations were heard at both lung bases *Bilateral inguinal adenitis also appeared* and the *rash became* confluent and spread to the arms and legs Albuminuria occurred during the third week Temperature began to fall on the eighteenth day and was normal by the twenty third day Thereafter convalescence was uneventful

Induced Resistance of Central Nervous System to Experimental Infection with Equine Encephalomyelitis Virus R Walter Schlesinger Peter K Olitsky *and Isabel M Morgan*[6] *(Rockefeller Inst) report that* although vaccination of guinea pigs with formalin inactivated Western equine encephalomyelitis virus rendered them specifically immune to an intracerebral challenge dose of 1 000 M L D of Western virus it failed to protect the central nervous system against the initial effects of the virus The intracerebral challenge dose was followed by an abortive infection of 20–30 hours duration characterized by fever and histopathologic changes which simulated the response of nonvaccinated control animals at that early stage

During the abortive infection of immune animals virus could occasionally be demonstrated in their brains indeed it was detected with about the same frequency that it was isolated from the brains of similarly inoculated nonimmune guinea pigs during the corresponding phases of the infection About one week after the abortive infection a marked transitory accumulation of specific neutralizing antibody was found in the brain tissue The ratio of brain antibody titer to serum antibody titer equaled at this time 1 1 or 1 10 instead of the value of about 1 300 found under physiologic conditions

Guinea-pigs which had recovered from an abortive infection with Western virus were resistant for a limited period to the effects of intracerebral inoculations of the immunologically distinct viruses of Eastern equine encephalomyelitis or vesicular stomatitis

Dimethyl Phthalate As a Repellent in Control of Phlebotomus (Pappataci or Sandfly) Fever Cornelius

(6) J Exp Med 80 197 11 September 1944

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(5) M J A st 1 ? 138 Aug 5 1944

CASE 2—Girl 2 had headache fever (104 F) stupor muscular twitchings clonic convulsive movements splenomegaly and rash following tick bite Urine showed hyaline and granular casts blood showed serum hypoproteinemia and agglutinated Proteus OX_{19} in a dilution of 1 320 She was given 1 7 0 cc whole blood 1 050 cc plasma and 2 400 cc other fluids, with prompt improvement Restoration of blood chlorides ended the convulsive movements restoration of plasma protein caused disappearance of edema. Fever persisted 5 days neurologic changes (spasticity bilateral positive Babinski signs and choreo athetoid movements) were still evident at discharge 2½ months later

CASE 3—Boy 15 had headache generalized muscle aching sore throat rash *meningeal signs with papilledema and coma* Temperature was 105 F blood pressure 80/58 There was no history of tick bite Proteus OX_{19} agglutination and Rocky Mountain spotted fever complement fixation tests were positive Spinal fluid gave a positive Pandy reaction the blood showed serum hypoproteinemia and van den Bergh reaction ranging from 2 to 11 mg per 100 cc Urine tests showed a nitrogen excretion mostly as urea equivalent to destruction of 561 Gm dry protein or 7 lb skeletal muscle in 78 hours Fifty cc hyperimmune rabbit serum was given without benefit Massive intravenous therapy with as much as 1,500 cc plasma in nine hours restored blood pressure and lumbar punctures relieved stupor and periodic apnea.

Intravenous supportive therapy in Rocky Mountain spotted fever has been condemned because of lack of appreciation of the underlying pathologic physiology Blood vessel endothelium and smooth muscle are damaged with resulting skin manifestations and changes analogous to those caused by burns Leakage of plasma water and crystalloids from damaged vessels produces hemoconcentration and circulatory failure Blood protein content is decreased owing partly to the leakage and partly to deficient synthesis in the damaged liver and this lowering of osmotic pressure causes further edema Administration of crystalloids or water in this phase may aggravate the situation whereas protein in the form of intravenous blood or plasma may be life saving Once peripheral circulatory collapse and hypoproteinemia are controlled fluids should be given parenterally to meet the particular need of the patient as determined by hematocrit readings blood count and blood chemical studies Blood chloride may be low Pre

B Philip (S C A U S) John R Paul (New Haven Conn) and Albert B Sabin (M C A U S) recommend dimethyl phthalate, an insect repellent for control of sandfly fever Its use during an epidemic showed it to be of value

The men in a given barracks were divided into two groups The repellent was issued to one group and an inert control solution to the other Men who decided not to take part in the experiment and some later arrivals then constituted a third group one using no repellent or control solution Directions for application of these solutions when the men retired were the same for the two groups Of the men receiving the repellent 42 per cent reported relief from bites of those receiving the control solution 12 per cent reported relief Two of the men receiving the repellent acquired sandfly fever during the five week experimental period 12 of those receiving the control solutions or no solution acquired sandfly fever Both men who used the repellent and acquired sandfly fever acknowledged that they had not followed directions and had failed to apply it for several consecutive nights prior to onset of the disease

Treatment of Rocky Mountain Spotted Fever A new approach to basic supportive therapy with particular reference to intravenous fluids is described by George T Harrell William Venning and William A Wolff[8] (Winston Salem N C) with report of three cases

CASE 1—Man, 45 had headache rash splenomegaly fever (106 2 F by rectum) and delirium following tick bite Blood serum agglutinated Proteus OX in a dilution of 1 160 Quinine 1.2 Gm daily was given for 3 days then metaphen 10 cc of a 1 1000 solution daily was administered for 10 day Glucose isotonic and hypertonic saline solution calcium and vitamins were given intravenously with repeated lumbar punctures to relieve headache Muscular twitchings and generalized edema accompanied by hypoproteinemia developed Pneumonia which developed th eleventh hospital day was treated by sulfadiazine without benefit and later by x ray The thirteenth day protein replacement therapy with blood and plasma transfusions was started edema disappeared and he began improving He was discharged the thirty fourth day

( ) W* M d 6 137 J ly 1944
(8) J A M A 1 8 9 934 Dec 9 1944

can substitute The tropical diseases may be divided into three groups

The first group consists of acute diseases which are not likely to be brought to Texas These include cholera yellow fever Rift Valley fever tsutsugamushi fever scrub typhus Australian Q fever epidemic typhus and boutonneuse fever They could be brought in as subclin ical or prodromal cases but are not a menace Both cholera and yellow fever have been present before and have disappeared

The second group diseases now endemic in Texas comprise dengue relapsing fever endemic typhus leprosy Bullis fever and of most concern malaria bacillary dysentery and amebiasis Many returning sol diers will have malaria for which the native anopheles mosquito is the vector Some of the plasmodium strains being brought into this country differ immunologically from those present here but give rise to similar clinical manifestations The effect of multiple strain infections has not been evaluated Latent infection may persist in Plasmodium malariae cases for 15–25 years in Plas modium vivax cases the most apt to relapse for 3 years and in Plasmodium falciparum cases for 1 year The last type may show repeated relapses with bizarre cerebral or gastro enteric manifestations Plasmodium ovale may be seen Bacillary dysentery may be intro duced through chronic cases or carriers The toxic Shiga strains common in Old World tropics and in Asia constitute a threat Use of sulfonamides will probably reduce the incidence of chronic cases and carriers Increase of amebiasis is unlikely though manifestations may be provoked in present subclinical carriers by sec ondary infection with foreign strains of intestinal bacteria

The third group consists of important diseases which may be introduced into Texas Plague and American Q fever are already endemic in the United States and so far are controlled African trypanosomiasis is limited even in Africa to certain areas having the tsetse fly

renal azotemia should be corrected by isotonic or hypertonic saline with or without glucose, isotonic solution of three chlorides, calcium chloride or sodium lactate

Hyperimmune rabbit serum (introduced by Topping) *is effective only if given early* *The liver should be protected* by a high protein, high carbohydrate diet supplemented by casec Amino acids given intravenously may help in regeneration of plasma proteins Vitamins should be given orally supplemented by intravenous administration of niacin ascorbic acid and thiamine hydrochloride

Choline Hydrochloride in Experimental Yellow Fever in Rhesus Monkeys A W Sellards and William S McCann[9] (Harvard Univ) report that of 14 monkeys (Macaca mulatta) inoculated with a potent yellow fever *virus which in 15 years had exhibited uniform lethal* properties 2 passage monkeys and 4 control monkeys died Eight monkeys received choline hydrochloride orally of these only three died

Examination of the livers of the monkeys that died revealed much more disorganization and acute liver destruction in those of monkeys not given choline hydrochloride The livers of the treated monkeys that died showed some evidence of a reparative process i e much less disorganization of the architecture and more proliferative changes in the periportal spaces

These experiments are not conclusive However they indicate that possibly the liver may be protected against a potent virus by oral administration of choline

Tropical Diseases in Texas in the Postwar Era *According to James A Greene and Wilton M Fisher*[1] (Houston), the diseases most apt to be brought back by troops are those with a chronic course, long incubation period or tendency to relapse Their establishment depends on *the presence of suitable vectors Careful* inspection and disinfestation of incoming craft preclude entry of vectors and it is improbable that local hosts

(9) U S Nav M Bull 43 4 0-422 September 1944
(1) Texas State J Med 40 408-41 December 1944

ing and typing of hemolytic streptococci isolated from patients with scarlet fever and (4) grouping and typing of hemolytic streptococci isolated from patients with rheumatic fever and from patients with respiratory infections antecedent to rheumatic fever

Statistics showed that the distribution of hemolytic streptococci throughout troop population is much greater in the Rocky Mountain and adjacent areas than in the southern parts of the country There were indication of great variations in percentage incidence of the hemolytic streptococcus and its component groups and types and in general a rather widespread distribution of those different components and no tendency for certain of the types to supplant completely all the *others in certain areas*

Bacteriologic studies on patients with upper respiratory infections showed Streptococcus haemolyticus types 19 17 30 3 1 36 and 6 associated with most of the infections However many other types were involved at all posts with significant incidence rates

Grouping and typing of hemolytic streptococci in 286 scarlet fever patients revealed group A hemolytic streptococcus in 229 with some 12 types present again types 1 3 17 19 and 30 were the most common

About 1 600 throat cultures were done on some 400 rheumatic fever patients at various stages of their disease The types obtained at individual posts paralleled closely the types observed in respiratory disease and scarlet fever Serial throat cultures were taken at seven day intervals in 74 rheumatic fever patients at Buckley Field in Colorado a post with a high incidence of rheumatic fever In only one case was the Lancefield type isolated at the first examination found at the second while 37 new strains appeared This ratio fell with succeeding cultures but clearly points out the impossibility of obtaining information regarding the bacteriology of the precipitating infection from pharyngeal cultures done after development of acute rheumatic fever under conditions existing at Army posts which have high incidence rates for streptococcic disease and

Cases brought in have shown no ability to spread South American Trypanosoma cruzi resembles trypanosomes infecting Texas kissing bugs (triatoma) and is harbored in the common armadillo and opossum No human infection has been reported so far Leishmaniasis exists in two forms visceral (kala azar) and cutaneous and is widespread throughout tropics and subtropics It is transmitted by the sandfly one species of which Phlebotomus diabolicus is present in Texas and may well become established A cutaneous case has already been observed in a local resident Among the schistosomes, the lung fluke is not a threat The blood fluke invades man while walking or swimming in water contaminated by infected snails No United States snail has been known to serve as host Wuchereria bancrofti and Wuchereria malayi filariasis are transmitted by mosquitoes the former by native species However Wuchereria bancrofti infection has been present in South Carolina for years and is gradually dying out Onchocerca volvulus (found in Central America), Dipetalonema perstans Mansonella ozzardi and Loa loa use flies as vectors None of the vectors are local inhabitants but related native species might become infected Dracontiasis is acquired through ingestion in drinking water of the infected small crustacean cyclops The native cyclops probably cannot be an intermediary

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STREPTOCOCCIC INFECTIONS

Geographic Distribution of Hemolytic Streptococci Arie C van Ravenswaay[7] (M C A U S) collected statistical material from eight Army Air Force installations with laboratories grouping and typing hemolytic streptococci so located as to represent areas of low incidence and areas of high incidence of rheumatic fever Attempts were made to obtain information on four main subjects (1) hemolytic streptococcus post survey (carrier) rates (2) incidence of hemolytic streptococci in patients hospitalized for upper respiratory disease (3) group

(7) J A M A 126 486 4 0 Oct 1 1944

results indicated that of all soldiers hospitalized for respiratory disease only 6 per cent had immunologic evidence of streptococcic infection although more than twice this number harbored beta hemolytic streptococci in their throats

Although this investigation was done in an area of low prevalence of beta hemolytic streptococci the criteria of illness due to this organism as established are applicable also to epidemic conditions

Chemoprophylaxis of Streptococcic Disease its benefits hazards and indications are discussed by Hugh J Morgan and Roy H Turner[4] (M C A U S) The success of mass chemoprophylaxis depends on the thoroughness and care of administration Sulfadiazine the preferred drug in daily 1 Gm doses has been used by the army and navy air forces with variable results the best being prevention of 9 out of 10 attacks of scarlet fever 5 out of 6 upper respiratory tract infections severe enough to necessitate hospitalization and virtually all pneumococcic pneumonia and meningococcic and gonorrheal infections

Mild reactions (commonly fever or rash) to prophylactic doses occur in about 0 5 per cent of cases and dangerous ones in 0 0001 per cent The most deplorable reactions have followed mistaken diagnoses and administration of therapeutic doses of sulfonamides to persons exhibiting manifestations of sensitivity Fever and chills have been diagnosed pneumonia rash scarlet fever and tonsillar or pharyngeal lesions from agranulocytosis an acute streptococcic infection A white blood cell count should be made before giving therapeutic doses of sulfonamides The physician should ask about possible recent chemoprophylaxis Transfusion of a sulfonamide sensitive patient with blood from a donor receiving prophylactic sulfadiazine has produced serious consequences

Individual prophylaxis is indicated during a group epidemic in which mass control is not available for per

(4) B ll N w Y k A d M d 1 37 43 J ry 1945

rheumatic fever At another post in Arizona which is an area of low incidence of rheumatic fever and streptococcic disease there was relative infrequency of acquisition of new strains of hemolytic streptococci and a tendency of the individual strain to persist

Further investigation showed a well defined tendency for streptococcic disease to occur more frequently at posts with high post survey rates than at those with low rates However even at posts with low survey rates for hemolytic streptococci the organism is found frequently in the upper respiratory infection which does occur A correlation also exists between post survey rates and the incidence of scarlet fever and of rheumatic fever

Role of Beta Hemolytic Streptococci in Common Respiratory Disease The Commission on Acute Respiratory Diseases[3] reports investigations made to evaluate the role of beta hemolytic streptococci by clinical cultural and serologic methods Examination of a large number of soldiers with respiratory diseases belonging to a military organization consisting chiefly of recruits showed that diagnosis of streptococcic disease depends on the combination of clinical signs bacteriologic findings and development of specific antibodies Presence of pharyngeal exudate alone was not a reliable guide since only half of such patients had streptococci by culture and only one fourth of them developed antibodies Of all patients with respiratory disease who harbored beta hemolytic streptococci in their throats only one third had streptococcic infection the other two thirds were carriers of the organisms and in these patients the streptococci had no etiologic relation to the respiratory disease True streptococcic disease occurred most frequently when pharyngeal exudate was present and typable group A strains of beta hemolytic streptococci were found by culture

Throat cultures obtained from healthy soldiers in the same military group showed beta hemolytic streptococci among 8 per cent Prevalence of group A strains in the same population was 5 per cent Cultural and serologic

(3) Am J Pub Health 35 6 5-68? J ly 1945

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sons subject to disabling respiratory infections such as sinusitis, bronchitis or bronchiectasis and for those with rheumatic fever The last should take sulfadiazine rigidly throughout the year without a summer lay-off

[We would question the advisability of such prophylactic use of sulfonamides first because of the doubtful efficacy and second because of the danger of deleterious effects of the drugs and the probability of producing drug fast strains of the organism concerned —Ed]

Studies on Nonhemolytic Streptococcus Isolated from Respiratory Tract of Human Beings Immunologic Relationship of Streptococcus MG to Streptococcus Salivarius Type I George S Mirick Lewis Thomas Edward C Curnen and Frank L Horsfall (M C U S N R) present results of cross agglutination quellung precipitation and complement fixation tests which clearly indicate that these two different nonhemolytic streptococci are immunologically related but antigenically distinct The immunologic relationship seems to be the result of the similarity of capsular structure the capsule of each organism being composed largely of a nitrogenous polysaccharide The authors had previously shown that, except only for Streptococcus salivarius type I streptococcus MG is serologically distinct from many other bacteria, including type specific pneumococci beta hemolytic streptococci and certain other nonhemolytic streptococci

It was also shown previously that streptococcus MG possesses numerous cultural characteristics widely distinct from those of Streptococcus salivarius and there is sufficient evidence to warrant the belief that they are different species of nonhemolytic streptococci The fact that the two organisms are immunologically related does not in the authors opinion militate against this assumption for many other distinctly different microbial species also possess polysaccharide antigens which are immunologically related

(5) J Exper Med 80 431 440 November 1944

Immunity to Tetanus Induced by a Third Dose of Toxoid Three Months to Four Years after Basic Immunization is reported by M. Murray Peshkin[6] based on a study of 159 allergic children Basic immunization was obtained with two 0 5 cc doses of combined alum precipitated diphtheria and tetanus toxoids The third dose consisted of 0 5 cc of either combined alum precipitated toxoids given to 98 children or alum precipitated tetanus toxoid alone given to 61 children The antitoxin level was determined at intervals after the second and the third doses of toxoids and the respective totals of 747 and 800 blood serum specimens were titrated for tetanus antitoxin Temperature elevation for one or two days followed administration of the third dose of combined toxoids in 11 per cent of the children as contrasted to 1 per cent in the group given only the two basic doses of combined toxoids The longer the interval between the second and the third dose the higher the incidence of febrile reaction (from 3 to 33 per cent in the respective groups of children given combined toxoids at intervals of 3–15 months and 3 years after basic immunization)

Two systemic allergic reactions urticaria and allergic rhinitis occurred during active immunization of 186 allergic children who had two or more doses of combined toxoids or tetanus toxoid alone an incidence of 0 37 per cent in 534 injections Children given alum precipitated tetanus toxoid alone gave no allergic or febrile reactions Scratch tests with the undiluted toxoid preparations were negative

The intervals between the two basic doses of combined toxoids and between these and the third dose have a direct influence on the antitoxin response The longer the intervals (up to three years) between the injections of toxoid the higher the antitoxin response Within one

(6) J Mt H p 1 555 566 M I 1945

month an adequate tetanus antitoxin titer developed in all cases this was higher and lasted longer than that which followed basic immunization

Peshkin recommends that the alum precipitated tetanus toxoid alone should be used as the third dose in a child who has had basic immunization with two doses of combined alum precipitated diphtheria and tetanus toxoids this keeps local and systemic allergic reactions at a minimum

Tetanus Occurring in Immunized Individual W Orr Goehring[7] (Pittsburgh) reports a case

Soldier 28 was in shock when hospitalized 1½ hour after he had intentionally shot him elf in the abdomen. He was conscious and stated that he had had three tetanus toxoid injections in the army Pla_ma was administered. Laparotomy di closed laceration of the spleen perforation of the liver and a rent in the gastrohepatic omentum with profuse bleeding from the spleen Autotransfusion of blood from the abdominal cavity was started splenectomy was performed and rents in liver and omentum were sutured The condition was considerably improved postoperatively A stimulating dose of fluid tetanus toxoid was ordered but was not obtainable Postoperative condition continued good until the second day when he seemed to be frightened and twitching of the facial muscles and later of the mu cles of the arms and upper body was noticed Trismus and risus sardonicus appeared there was rigidity of the upper arms and abdominal muscles and reflexes of the legs were greatly exaggerated Respirations became labored and the patient was slightly c anotic Diagno is of tetanus was made He was placed in an oxyg n tent and given paraldehyde by rectum and 100 000 units of tetanus antitoxin 60 000 units intravenou ly and 40 000 units intramuscularly The condition however continued to grow wor e generalized convulsions developed and death occurred 60 hours after admis ion Permission for autopsy could not be obtained

Despite absence of bacteriologic confirmation the diagnosis of tetanus seemed well established Rabies strychnine poisoning and reaction to autotransfusion could be ruled out As suggested by Boyd failure of active immunization to tetanus might have three explanations (1) some individuals may not react to immunization (2) the circulating antitoxin may be small in quantity and may remain so for a week after injury and (3) in

( ) Am J Su g 46 1 3 1 O t be 1944

badly wounded and shocked subjects antitoxin production may be less Goehring suggests administration of tetanus antitoxin in all cases of shock severe hemorrhage extensive tissue damage etc to supplement active immunization This procedure has been adopted routinely by the British army

Fatal Case of Tetanus Despite Toxoid is reported by C A. de Candole[8]

Anglo Indian 40 was seen February 7 for prolapsed inflamed and ulcerated hemorrhoids These were ligated and excised 10 days later under stovaine analgesia Six days after operation uncontrollable jerking of the legs began followed in three days by spasms of the abdominal muscles and fever The next day the neck and jaw were stiff and infrequent opisthotonic spasms of short duration began March _ fully developed tetanus was present with severe spasms each lasting a second or two and recurring every half minute or less Specific treatment consisted of 1 cc tetanus toxoid and of 1 010 000 I U of serum given over four days Avertin and intravenous nembutal were used symptomatically The patient died March 5 Autopsy revealed nothing aside from bronchopneumonia The operative wounds were healed. The patient had received two tetanus toxoid inoculations over three years previously

Although not proved bacteriologically the clinical course in the case suggests that the anal region was the source of infection and that the tetanus bacilli were introduced at operation The patient obviously did not have a high level of circulating antitoxin De Candole suggests as a reasonable precaution that a recall dose of toxoid be given such patients a week before operation and that operation for internal hemorrhoids be delayed

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TULAREMIA

Tick Borne Tularemia George V Byfield Lawrence *Breslow* Roland P *Cross Jr* and *Noel J Hershey*[9] (M C A U S) report 15 cases in soldiers from an Army maneuver area in Tennessee observed within 30 days Ten of the 15 had a definite history of tick bite and all had been on maneuvers sleeping on the ground in pup tents There was an interval of one to nine days between

(8) B t M J 1 97 98 M 3 1945
(9) J A M A 127 191 196 J n 7 1945

known tick bite and onset of symptoms First symptoms ranged from moderately severe chills followed by high fever, severe headache backache generalized muscular soreness and soreness of the bones to general malaise and symptoms similar to mild influenza Pain and tenderness in the area of regional lymphadenopathy was frequent

Examination showed the patients to be febrile, some with mild dehydration and characteristic tularemic lesions of the skin There was evidence in most patients of multiple insect bites attributed to chiggers, mosquitoes, ticks or a combination of these The lesions the punched out or ragged ulcers and the regional lymphadenopathy varied in location Earliest tularemic lesions noted were areas of skin 2–3 cm in diameter showing central necrosis and ulcerations The early ulcer was usually surrounded by erythema which later underwent necrosis to some extent The leg was the commonest site of typical ulcers Thirteen of the patients had large masses of tender regional lymph nodes inguinal or subinguinal in 9 and axillary in 4 Abscess formation of the lymph nodes developed in some patients In one patient pleural effusion and pneumonia developed and in another nuchal rigidity and a positive Kernig sign with normal cerebrospinal fluid

Treatment was symptomatic in most cases although one patient received metaphen, three patients had surgical drainage of abscesses and six patients had received sulfonamides before and two after admission

Efficacy of Some Drugs and Biologic Preparations As Therapeutic Agents for Tularemia J Frederick Bell and Oscar B Kahn[1] (Wayne Univ) discuss the many contradictory reports on the efficacy of various therapeutic agents used in treatment of tularemia and report results of experiments with guinea pigs infected with tularemia and treated with these drugs The materials included sulfanilamide sulfadiazine sulfamerazine acriflavine metaphen iodide and bismuth (iodobismitol

(1) Arch I t Med 75 155 158 Ma h 1945

with saligenin) arsenic and bismuth (solution of bis muth subgallate and sodium para aminophenyl arson ate), trivalent arsenic alone (mapharsen) antimony stibophen penicillin and hyperimmune equine antitu laremic serum All substances penicillin possibly ex cepted were used in amounts which proportionately exceeded the doses given human subjects The results of these therapeutic trials do not demonstrate any ad vantage in using these drugs in treatment of tularemia

PENICILLIN

Action of Penicillin on Bacteria Lawrence P Garrod (Univ of London) reports experiments which show that penicillin is fairly rapidly lethal to susceptible bacteria This action is accelerated by increase in temperature throughout the range 4–42 C It is progressively im paired by increase in the acidity of the medium between pH 7 0 and 5 0 Purity of the penicillin material is of importance All commercial penicillins tested were less active in high than in low concentrations presumably due to the impurities present The experiments further showed that there is no advantage in using high concen trations of penicillin especially in local treatment Al though it is true of other therapeutic agents that the greater the dose the more certain the effect the reverse appears to be true of penicillin A concentration of 1 unit per ml is not only as effective as one of 1 000 units but often more so The only plausible reason for using strong solutions in local treatment is to insure that loss by escape dilution or absorption does not permit the concentration to fall below the minimal level for full effect which may be taken as about 0 1 unit per ml The standard optimal strength of a solution probably need not exceed 250 units per ml

The experiments with penicillin in diluted broth and in the presence of bacteriostatic agents lend support to the hypothesis advanced by Bigger that the drug acts only on dividing cells however the effect of tempera

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(1) Arch Int Med 75 155-158 March 1945

tubes are stuck in plasticine and incubated horizontally overnight They are examined over a black background or after standing upright for an hour in which case the undissolved corpuscles settle giving a beautiful end point

Both methods can be used in estimating penicillin in other body fluids and are especially valuable when only minute quantities of fluid are obtainable Pus can be tested by centrifuging it and titrating the supernatant fluid or if the pus is so thick there is no supernatant fluid saline can be added to the pus allowed to stand and then centrifuged The presence of organisms other than hemolytic or penicillinase producing organisms does not interfere with the test

Penicillin Content of Blood Serum after Various Doses of Penicillin by Various Routes was determined by A Fleming M Y Young J Suchet and A J E Powe[4] (St Mary s Hosp London) The methods used for estimations have been described by Fleming [see preceding article] After intramuscular and subcutaneous injections penicillin appeared in the blood within a few minutes but did not reach as high concentration as when given intravenously (maximum 0 5 units per cc versus 4 units) Disappearance from the blood occurred slightly sooner after intravenous administration Penicillin was excreted in the urine so rapidly that the urine contained high titers in one instance about 400 units per cc

The quantity of penicillin injected affected the maximal concentration from 0 5 units per cc after 15 000 units given intramuscularly to 2–3 units after 100 000 units and also increased the duration in the blood stream With 15 000 units penicillin disappeared in two to three hours with 100 000 units in five to six hours Injection of 15 000 units intravenously or intramuscularly at 10 or 15 minute intervals produced higher titers than single injections

Intravenous and intramuscular drip administration maintain a constant level the height of which depends on the rate of flow of penicillin Penicillin administered

(4) L et 6 16 4 N 11 1944

ture and the almost uniform susceptibility of cells from both old and very young cultures are against this hy pothesis

Micromethods of Estimating Penicillin in Blood Serum and Other Body Fluids by titration of bacterio static power are described by Alexander Fleming[3] (St Mary's Hosp London)

TECHNIC —*Slide Cell Method* —Slide cells (modification of Wright s technic 192ↄ) are prepared by treating strips of paper 0 2 mm thick and 2 5 mm wide with soft paraffin and placing them on a slide to divide it into six compartments Slides need not be sterile The upper slide covering the cells can be slid back about 1 mm to permit filling of compartments The indicator is human blood preferably group O to which liquoid has been added in concentrations of 1 1 000 or 1 2 000 to destroy leukocytes and prevent clotting One cc of this is seeded with 5 cu mm (or a large loopful) of a 24 hour broth culture of a powerfully hemo lytic easily cultured profusely growing streptococcus Sensitivity must be standardized before the test by titrating a solution of 0 5 unit penicillin per cc blood serum in the same way as in the test Paraffined slides are made by spreading heated paraffin wax (130–140 C) in a thin layer over the slides and allowing it o cool

A series of ∠5 cu mm normal saline drops are placed on a par affined slide To the left is put °ↄ cu mm of the patient s serum Another 25 cu mm of serum is mixed with the first drop of saline and of this mixture 25 cu mm is mixed with the next and so on the next to last 25 cu mm being discarded The drops now represent dilutions of serum of 1 1, 1 2, 1 4 1 8 etc with the last drop a control containing only saline Then 2ↄ cu mm infected blood is mixed with each dilution and the mixture or part of it transferred to slide cells Slide cells are placed 1–2 mm apart on a glass plate and sealed with heated paraffin wax and soft paraffin in equal parts They are incubated overnight at 37 C and examined horizontally by transmitted light When there is sufficient penicillin in the serum to inhibit streptococci, the blood is unchanged When there is no inhibition the blood is completely hemolyzed

Capillary Tube Method —Materials resemble those used in the preceding method except that the blood is diluted with an equal volume of saline before being infected with hemolytic streptococ cus and only 5 cu mm infected blood is mixed with each of the 25 cu mm serial dilutions of patient s serum on the paraffined slide The drops are taken up in capillary tubes 3 in long and of even caliber about 0 8 mm in diameter By tilting the tube the fluid is run to the middle then the ends are sealed in flame The

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hours with a decrease to a level of 1.6 units per ml eight hours after administration. Blood levels of about 0.05, 0.04, 0.04, 0.02 and 0 units of penicillin per ml were obtained from one, two, four, six and eight hour bleedings. This and other trials in human beings and dogs indicate that detectable blood level of penicillin may be maintained for considerable periods after oral administration of a single dose of penicillin in oil. If the range of 0.03–0.06 units of penicillin per ml blood is considered the mean value as established by clinical practice, then a single oral dose of 90,000 units of penicillin in oil will maintain a fairly uniform therapeutic blood level for at least four hours. Two or possibly three injections of 20,000 units of an aqueous solution of penicillin would be necessary to maintain a comparable blood concentration over the same period. Further experimentation showed that oral administration of 90,000 units of penicillin in oil and two subsequent doses of 20,000 units each given three and six hours later to a human being maintained the therapeutic blood level for at least seven hours and only slightly less than a therapeutic level was found after eight hours. Administration of the oral doses on an empty stomach increases the possibility of maintaining the optimal blood levels.

Thus, although greater amounts of penicillin are needed, oral administration is possible and has the advantage of being simple.

[It is probable that enteric coated preparations of penicillin suitable for oral administration will be on the market soon.—Ed.]

Enhancement of Plasma Concentration of Penicillin in Dogs by Simultaneous Administration of Para Aminohippuric Acid. Karl H. Beyer, W. F. Verwey, Roland Woodward, Lawrence Peters and Paul A. Mattis[6] (Glenolden, Pa.) report their third investigation of the effect of simultaneous administration of the sodium salt of para aminohippuric acid and penicillin on plasma concentration and renal elimination of penicillin. The experiments on dogs showed that the two drugs could be administered continuously for at least 48 hours with

(6) A. J. M. S. 09 608 6 1 M 194

by intramuscular drip did not appear in the blood for 30 to 60 or more minutes, depending on the dosage Administration of 60 000 units in 24 hours gave low but adequate levels as determined by patients recovery In one case 240 000 units in 24 hours yielded 0 5 units per cc blood serum throughout administration

It is not known whether continuous low levels or intermittent high levels are preferable Clinically, both systems have worked excellently Intramuscular drip is the most economical method of giving penicillin In cases in which operation is to be done through septic tissue 100 000 units injected 15 minutes before will provide an advantageous high concentration

Penicillin made up in 1 per cent procaine produced results similar to penicillin in saline with the advantage of painless injection Two patients with kidney disease showed a much higher concentration and longer retention of penicillin than the other patients

Oral Administration of Penicillin in Oil Raymond L Libby (Stamford Conn) calls attention to experimental data reported in the literature which shows that not all penicillin activity is lost in the stomach and that *penicillin can be absorbed from the small intestine* Libby therefore experimented with various extraction and purification procedures for penicillin and solutions of penicillin either as suspensions or dispersions to find a material which could be given orally Oil suspensions of the sodium and calcium salts of penicillin 150–300 units per mg were prepared in cottonseed oil and dispensed in gelatin capsules made up to contain 10 000 25,000 and 50 000 units per capsule A single dose of about 90 000 units of sodium penicillin in such a capsule was given a man weighing 86 kg the first urine sample taken 25 minutes after administration contained about 0 4 units of penicillin per ml indicating a fairly rapid passage of the drug in the oil through the stomach and absorption from the intestine Maximal amounts of penicillin were found in the urine during the first two

(5) Sc nce 101 178 180 F b 16 1945

respect than is either sulfanilamide or sulfapyridine

Whether sulfathiazole would prove as valuable in vivo as it has been demonstrated to be in vitro can be decided only by clinical trial but in view of the results in the experiments recorded such trials would be worth while The simultaneous administration of sulfathiazole and penicillin (if they behaved in the same way in vivo as in vitro) not only would control the infecting bacteria as well as a double dose of penicillin without sulfathiazole but would also prevent to a considerable extent any multiplication of bacteria at those periods when the penicillin concentration in the blood is low

Clinical Experiences with Penicillin Wendell J Stainsby Harold L Foss and John F Drumheller[8] (Danville) present clinical results from extensive use of penicillin at Geisinger Memorial Hospital

Patients with meningitis received 10 000–30 000 Oxford units intraspinally usually at 24 hour intervals dosage depending on seriousness of the condition Supplemental intramuscular injections were given in each case Patients without meningeal involvement were given 15 000–20 000 units every three hours For surface infections such as burns necrotic ulcers or infected wounds compresses saturated with a solution of calcium penicillin in a concentration of 250 units per cc water were applied four times daily or an ointment composed of 250–500 units per Gm dissolved in a water soluble base known as hydrosorb was applied twice daily The latter method was best because there was less wastage of penicillin and the penicillin was held closely to the infected area for longer time Another advantage was that the ointment could be stored either at room temperature or in the refrigerator For large abscesses and empyema rubber tubes were inserted in one or two counter openings Skin edges were approximated tightly around the tubes by sutures and a solution of 250 units of penicillin per cc distilled water was injected twice daily Rib resection was sometimes necessary for inser

(8) Pennsyl i M J 48 1191 5 N v mb 1944

out occurrence of morphologic or functional changes directly attributable to the two compounds Intravenous administration of para aminohippuric acid to maintain plasma concentrations of about 30 mg per 100 cc invariably resulted in an increase in penicillin plasma concentration of two and one half to four times the basal level, even though penicillin concentration was not varied The stepwise increase in plasma para amino hippuric acid concentration above the level of 30 mg per 100 cc resulted in a further, but not commensurate elevation of the penicillin plasma level The effect of para aminohippuric acid in increasing the plasma concentration of penicillin was always reflected in a decrease in the renal clearance of penicillin Since para aminohippuric acid did not appear to be nephrotoxic by any of the tests used the findings support the theory that the effect of this compound is purely one of physiologic competition with penicillin for a common renal tubular excretory mechanism This process has been visualized as one involving a common transport system across the renal tubules in which the competition between the two substances for this common carrier is probably one of mass action, and in which relative affinities of the two substrates for the same system play an undetermined role The whole process is a dynamic one which shifts rapidly as the plasma concentration of either component is varied within certain limits

Synergic Action of Penicillin and Sulfonamides Joseph W Bigger[7] (R A M C) records experiments in which sulfathiazole in serum as well as in broth rendered effective as an inhibitory agent against staphylococci a concentration of penicillin which was ineffective without sulfathiazole The degree of synergic action varied considerably with the strain of organism but was obvious even when no inhibitory action of sulfathiazole alone could be detected The action of penicillin against Streptococcus pyogenes is similarly reinforced by sulfathiazole Sulfathiazole is more effective in this

(7) Lancet 2 14 145 July 9 1944

mia 240 000 units daily for 12–20 days osteomyelitis 160 000 units daily for 20 days sinusitis and mastoiditis 120 000 units daily for 12 days carbuncles furuncles and cellulitis 120 000 units daily for 6 days tonsillitis and peritonsilar abscess 80 000 units daily for 5 days and peritonitis 240 000 units daily for 10 days Duration of treatment was determined by clinical response and laboratory observations

The sodium salt was used and incidence of reactions was low regardless of length of treatment Reactions included mild fever burning pain at injection sites generalized edema and urticaria

Effectiveness of penicillin was influenced both by the character of the lesion and by the causative infectious agent The conditions treated included infections caused by gonococci meningo occi pneumococci staphylococci and streptococci and various mixed infections One hundred per cent cure was obtained among 1 000 patients with gonorrhea 97 per cent being cured after the first course and the remaining 3 per cent after the second Five patients with gonococcic arthritis responded to treatment Three patients with meningitis and bacteremia recovered after treatment with intrathecal and intramuscular injections and two patients with meningococcic bacteremia only were cured Ten patients with pneumococcic pneumonia recovered and three with pneumococcic empyema recovered without surgical intervention Of nine patients with staphylococcic bacteremia seven recovered the two deaths resulting from bacterial endocarditis Of 27 patients with osteomyelitis all but 2 recovered with surgical treatment an important factor in the cure of 25 Staphylococcic infections of the accessory sinuses were present in 12 patients 4 did not recover because of chronicity of the process A total of 18 patients with staphylococcic cellulitis and 2 patients with staphylococcic pneumonia and empyema recovered without recourse to surgery Hemolytic streptococcus infections included severe ear nose and throat infections empyema and osteomyelitis All pa

tion of the tubes in empyema In no case was there significant reaction to penicillin

Three patients with meningococcus meningitis died two of them having been admitted in moribund condition, and three recovered The authors consider sulfadiazine the first choice in treatment of meningococcus meningitis but in the extremely ill and those who do not respond to the drug penicillin should also be used One patient with streptococcus septicemia recovered under penicillin therapy after discontinuance of sulfadiazine because of serious kidney complications The most dramatic results were obtained in four patients with Staphylococcus aureus septicemia and one with Staphylococcus aureus meningitis In the only patient of this group who died, a secondarily infected carcinoma of the colon had ruptured through the diaphragm into the lung The authors found the sulfonamides of little therapeutic value in staphylococcus septicemia They consider it particularly important to search for the primary factor in such cases and to establish adequate drainage Globulin modified staphylococcus antitoxin may be used as supplement to penicillin Two patients with pneumonia caused by mixed infection of hemolytic streptococcus and Staphylococcus albus failed to respond to sulfadiazine but recovered with penicillin The drug was effective in two patients with acute gangrenous appendicitis with rupture and in another with a long standing osteomyelitis Sodium penicillin was generally used for medical cases and calcium salt for surgical cases, no special *difference was noted in their action*

Penicillin Program at the United States Naval Hospital, Portsmouth Va Herbert J Fox[9] reports on the effectiveness of penicillin usually given intramuscularly in 29 different diseases The penicillin requirements for some of the diseases were found to be gonorrhea 80 000–100 000 units in 1 day pneumococcic pneumonia 80 000 units daily for 5 days empyema 50,000 units daily for 3–5 days staphylococcic bactere

(9) War Med 7 170 17 M h 1945

of infection have disappeared Acute osteomyelitis can be treated satisfactorily without surgical intervention provided penicillin therapy is begun early enough and before abscesses of the soft parts or extension of the in fections of the joints has developed The drug must be given in amounts of 120 000–250 000 units daily and continued until all clinical signs have disappeared Pa tients with bacterial endocarditis due to susceptible or ganisms such as the staphylococcus pneumococcus hem olytic streptococcus and Streptococcus viridans should be treated with penicillin treatment continuing for at least three to eight weeks with 200 000–300 000 units daily

In gas gangrene best results are achieved with a com bination of antitoxin penicillin and surgical removal of necrotic and damaged tissue The recommended dose of penicillin is 15 000 units every three hours for 3–4 days for control of infection in cases in which all infected tissue can be removed surgically If this is impossible treatment should be continued for 5–10 days

Final evaluation of results of penicillin therapy in syphilis is not yet possible Preliminary reports indicate that a course of 60 injections of 20 000 units each given intramuscularly at three hour intervals for 7½ days probably is the minimal schedule effective in controlling primary and secondary syphilis The Herxheimer reac tion characterized by fever malaise headache intensi fication of eruption and painful swelling of the primary lesions and regional lymph nodes is not a contraindica tion to continuing treatment with penicillin

Although penicillin is considered a nontoxic drug cer tain side reactions do occur These include urticaria ves icular eruptions pain on intramuscular injection thrombophlebitis of the veins at the injection site and abdominal cramps with or without diarrhea nausea and vomiting So far no permanent harmful effects on any of the systems of the body have been recorded At pres ent there are no known contraindications to administra tion of penicillin although there may be reason for giv

tients with these infections recovered Mixed infections included acute generalized peritonitis (all patients cured) localized peritonitis (all patients cured), cellulitis of the jaw (7 of 9 cured) and nonvenereal prostatitis (10 of 14 cured the 4 failures being due to infection with resistant nonhemolytic streptococci) There were six patients with miscellaneous diseases Treatment failed in tuberculous meningitis, rheumatic fever, enterocolitis chancroid and sycosis vulgaris One patient with subacute bacterial endocarditis was treated but death resulted from a resistant nonhemolytic streptococcus

Penicillin in Treatment of Infections Chester S Keefer[1] (Boston Univ) states that the gonococcus is the most sensitive of all organisms to penicillin, 98 per cent of all gonococcic infections of the lower genital tract in men and women being amenable to administration of 100 000 units of penicillin over 24 hours The remaining 2 per cent respond frequently to more intensive and prolonged treatment There have been no proved cases of penicillin resistant gonorrhea In treatment of meningococcic meningitis sulfadiazine continues to be the drug of choice since response to penicillin is slower than that to the sulfonamides The pneumococcus is extremely susceptible to penicillin in vitro Prognosis is excellent for pneumococcic lobar pneumonia treated with penicillin Dosage is gaged by the condition and response of the patient Pneumococcic meningitis always a serious disease apparently responds best to a combination of sulfadiazine and penicillin

The hemolytic streptococcus is also highly susceptible to the action of penicillin which is the drug of choice in all hemolytic streptococcus infections treatment must be continued until clinical recovery is complete Penicillin is also the drug of choice in all staphylococcic infections with or without bacteremia Patients should be treated early and should receive between 100 000 and 200 000 units daily for two to three weeks until all signs

(1) West J Surg 53 93 10 Ap il 1945

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ing small initial doses to patients with cardiovascular extragenital syphilis

Effectiveness of Penicillin in Treatment of Vincent's Angina Bernard M Schwartz (M C A U S) reports 14 cases in which diagnosis was established by positive clinical and laboratory findings Penicillin was injected intramuscularly in each case The first two patients were given a total of 200 000 units of the sodium salt of penicillin administered in 20 000 unit doses every three hours The response was so satisfactory that in all subsequent cases with three exceptions the dosage was reduced to 100 000 units given in 20 000 unit doses every three hours The three exceptions consisted of one moderately severe case in which two doses of 50 000 units were given six hours apart and two mild cases in which a total of 50 000 and 25 000 units respectively was given in one dose The larger doses of 100 000 units with 20 000 units every three hours were considered preferable

Results in each case were satisfactory Subjective discomfort disappeared quickly and there was definite improvement in four to six hours after institution of treatment Smears positive before treatment became negative Improvement in appearance of lesions was definite but not as dramatic as subjective improvement The first change was one in color and character of the exudate It changed from dirty gray or yellow to a clean whitish gray film which did not bleed The exudate and ulcer completely disappeared in 1–10 days Simultaneously adenopathy gradually subsided Gingivitis rapidly disappeared and temperature became normal after 24 hours There were no recurrences

Use of Penicillin in Vincent's Angina Paul L Shallenberger, Earl R Denny and Harold D Pyle[3] (M C A U S) divided patients with an established diagnosis of Vincent's angina into four groups Group 1 (13 patients) was treated variously with hydrogen peroxide sodium perborate chromic acid silver nitrate and ma

(2) J A M A 1 8 04 06, July 7 1945
(3) Ibid pp 706 710

pharsen group 2 (11 patients) with 1 Gm sulfadiazine every four hours in lozenge form group 3 (9 patients) with penicillin by local application in a concentration of 250–500 units per cc four times daily and administration of 5 gr acetylsalicylic acid as needed for pain and group 4 (2 patients) with penicillin intramuscularly dosage being 15 000 units in a concentration of 10 000 units per cc every three hours for eight doses

In group 1 most of the smears did not become negative until the seventh to twelfth day of administration of the various agents In group 2 most of the smears became negative by the seventh or ninth day after administration of sulfadiazine In group 3 clinical and bacteriologic responses were striking Subjective and objective improvement occurred quickly With the exception of one case the smears became negative by the fifth day average time for disappearance of Vincent s organisms was 3 7 days after institution of penicillin therapy The first patient of group 4 who had a severe attack showed definite improvement within 48 hours and repeated smears were negative on the third day of treatment The second patient of this group also was severely ill improvement began six hours after the first dose of penicillin had been given Fusiform bacilli and spirilla completely disappeared from the infection site 12 hours after start of treatment when the patient had received 60 000 units

Penicillin given intramuscularly every three hours for eight doses is a rapidly effective method of treatment of Vincent s angina as is the topical application of penicillin in a concentration of 500 units per cc four times daily

Effect of Penicillin on Rheumatoid Arthritis E W Boland N E Headley and P S Hench[4] (M C A U S) gave penicillin to 10 soldiers with early but progressive rheumatoid arthritis The drug was given intramuscularly every three hours day and night Daily doses ranged from 120 000 to 320 000 Oxford units and total dosage from 1 800 000 to 3 250 000 units in 14–20 days

(4) P St ff Me t M yo Cl n 19 505 506 Oct 18 1944

Clinical results were essentially negative seven patients experienced no significant improvement, one felt worse and two showed some improvement which could not be attributed to the treatment No change in sedimentation rate, leukocyte count or synovial fluid occurred Improved appetite in six patients may have been unrelated to penicillin or may have been a side effect thereof

Results of the study do not support the idea that hemolytic streptococci may be etiologically related to rheumatoid arthritis likewise it may be assumed that the disease is not caused by any bacteria known to be rapidly affected by penicillin

Penicillin in Treatment of Experimental Infections with Bacillus Anthracis Although anthrax has decreased in incidence and fatality in humans it still is an important problem in certain industries There is no agreement as to the best treatment of experimental or clinical anthrax Use of serum arsenicals or sulfonamides may at times cause untoward side effects Because of the low toxicity of penicillin for animals and man, and because of the sensitivity of Bacillus anthracis to penicillin as demonstrated by Oxford investigators I R Heilman W E Herrell and Constance Carter[5] used penicillin in experimental anthrax induced in mice

Treatment was administered subcutaneously in divided doses at the rate of 1 000 units per day both sodium and calcium penicillin were used Treatment was not given at night In the first experiment the mice were inoculated with 0 05 cc of a suspension of Bacillus anthracis diluted to a density of tube no 3 on the McFarland nephelometer Treatment was started 16 hours after inoculation and continued for 12 days All mice in an untreated group died most of them on the first day after inoculation Of the treated mice 45 per cent died This mortality rate among treated mice was attributed to the large number of bacteria introduced (10 000 times the lethal dose) Other contributing factors were thought to be the

(5) Proc St ff Meet M y Clin 19 49 -496, Oct. 4 1944

late beginning of treatment after inoculation when many mice had already developed dependent edema at the site of inoculation, and the discontinuation of treatment at night

In a second experiment animals were inoculated with 0 05 cc of a 1 1 000 dilution of the same suspension of the organism as used in the first experiment Treatment was started one hour after inoculation and continued for 12 days None of the treated mice developed edema at the site of inoculation or evidence of illness during the 26 days *period of observation All untreated mice in* this experiment had dependent edema the day after inoculation and all died within four days after inoculation whereas none of the treated mice died

The results indicate that infections with Bacillus anthracis are susceptible to treatment with penicillin

Treatment of Diphtheria Carriers with Penicillin B B Berman and S H Spitz[6] point out that carriers of Corynebacterium diphtheriae are particularly dangerous among military personnel since Schick testing of troops has shown that about 30 per cent are susceptible to diphtheria Treatment of carriers with the sulfonamides has been unsatisfactory but since experiments with penicillin indicated promising results it was used in treatment of 10 proved diphtheria carriers

A patient was considered a carrier only if diphtheria organisms were found in culture of the nasopharynx for more than three weeks Of 22 such patients found 10 were treated by local application of penicillin to nose and throat and 12 served as controls Penicillin was dissolved in normal saline 500 Oxford units to 1 cc and with an ordinary nose dropper 1 cc of the solution was instilled *into both* nostrils four times daily for five days Immediately after instillation 1 cc was sprayed with an atomizer onto the fauces and posterior wall of the pharynx The total amount of penicillin used in each case throughout the five day course was 20 000 units Cultures of the nasopharynx were planted on Loffler s me

(6) Bull U S Army M D pt 4 87 91 J ly 1945

dium every other day after beginning of therapy until three consecutive negative reports were obtained No other treatment was used Patients in the control group were treated with hot saline gargles four times daily Cultures were taken at least every other day until three consecutive negative reports were obtained

In the 10 treated patients the throat cultures became negative during treatment or on the first day after cessation of therapy Follow up observation on eight patients showed the cultures to be negative four weeks later Of the control group cultures of seven reverted spontaneously to negative in the fifth week cultures of the other five continued positive for six or seven weeks after which these patients were used as treated controls With penicillin treatment similar to that originally given all of them became negative during the period of therapy or on the first day thereafter Follow up of six of them showed them to be negative

Although the number of cases is small the evidence suggests that penicillin is effective in the control of carrier states and valuable in shortening the quarantine period The rapidity with which the organisms disappeared from the nasopharynx indicates that penicillin may be used as an adjunct in treatment of clinical diphtheria it should not however replace antitoxin Concerning the method of application of penicillin possibly the instillation method into accessory nasal sinuses by the Proetz displacement procedure would be best since with this method nasopharyngeal tissues would be bathed continuously for 72 hours by seepage from the sinuses

Arrest by Penicillin of Two Cases of Subacute Bacterial Endocarditis, Due Respectively to an Anaerobic Staphylococcus and to Streptococcus Viridans In the first case reported by B S Oppenheimer and A Leonard Lubby,[7] Staphylococcus anaerobius a strictly anaerobic micro organism was isolated from the blood stream This organism had not been found previously in subacute bacterial endocarditis possibly because strictly

(7) J Mt Sina Hosp 1 541 554 May Ju e, 1945

anaerobic cultures are not usually made in this condition Two courses of penicillin were given in this case, totaling 5 200 000 units It was given first by continuous intravenous drip but later by intramuscular injection because of marked signs of retention of fluid despite digitalis and ammonium chloride administration The patient was discharged without signs or symptoms of subacute bacterial endocarditis i e no chills fever sweating or embolic phenomena and no symptoms of this condition had developed six months after discharge

The second case presented the familiar picture of chronic rheumatic cardiovascular disease with the typical phenomena of subacute bacterial endocarditis due to alpha Streptococcus viridans In this case the combination of penicillin and heparin after Loewe s method was used A total of 4 200 000 units of penicillin was given intramuscularly because congestive heart failure contraindicated the intravenous route 25 000 units was given every three hours in 3 cc saline totaling 200 000 units daily Heparin was given subcutaneously Nine months after discharge from the hospital the condition still seemed to be arrested and the patient was bacteria free

[While some cases of subacute bacterial endocarditis will yield to the e do es our expe ience lea ls us to bel eve that it is safer to begin with somewhere near 1 000 000 units per day —Ed.]

Penicillin in Gas Gangrene Report of Successful Use of Penicillin in a Clostridium Welchii Infection is made by Arthur A McAuley and Alonzo P Gearhart[8] (Wichita Kan)

Man 28 suffered a badly comminuted fracture of the right femur when hit by a bus He sustained no lacerations on the fractured leg but some on the other A cast was applied covering the entire right leg and extending to the knee of the left His condition afterward was good but because circulation of the affected leg seemed disturbed the cast was cut to above the knee and spread apart White blood cell count was 17 000 hemoglobin 14 5 Gm The next day discoloration was present up to the knee and later became worse The cast was bivalved its entire length disclosing discoloration with blebs on the anterior aspect of the leg Smears and culture showed Clostridium welchii Hemoglobin was now 8 Gm and white blood cell count 1 000 Ad

(8) J K n M S 4 416 418 D embe 1944

ministration of 1 Gm sulfadiazine every four hours proved inef fective On the fifth day amputation was considered but was not done because of the patient's poor condition. The skin appeared a tawny hue There was a blue area in the right midaxillary region and the right thigh and lower abdomen appeared dusky The back and face were edematous and the eyes swollen shut Pulse rate was 130

Sulfadiazine therapy was discontinued and the patient was given 500 cc whole blood 500 cc plasma and in the morning and afternoon penicillin 40 000 units in 1 L. of 5 per cent glu cose in normal saline by intravenous drip The following day he received another transfusion and 200 000 units of penicillin Penicillin therapy was continued and by the fourth day the patient appeared greatly improved Temperature had dropped and the gangrenous area had become localized A guillotine am putation was done 5 cm above the knee during which bubble of gas exuded from the fascia Part of the flesh appeared cooked Microscopic examination revealed gram positive rods but little inflammatory reaction Penicillin was then decreased to 150 000 or 100 000 units per day It was discontinued 12 days after the initial dose a total of 1,580 000 units having been given Con valescence was complicated by post transfusion reactions and cystitis and urethritis The thirty ninth day the patient was dis charged with a clean stump negative for Clostridium welchii

Penicillin has been proved valuable in experimentally produced clostridium infections and would seem equally valuable clinically No portal of entry for the infection was discovered in this case

Haverhill Fever Following Rat Bite Treated with Penicillin George Robins[9] (Louisville Gen l Hosp) re ports a case in which sulfonamide therapy was inef fectual but penicillin controlled temperature and bac teremia

Man 70 sustained a rat bite on the left wrist which was cauterized immediately The next day malaise and generalized aching developed followed at night by chills fever nausea and vomiting About 48 hours after having been bitten the patient was hospitalized in a septic and somewhat stuporous state Tem perature was 102 F pulse 1 0 and respirations 24 The site of the bite was surrounded by a small inflammatory reaction and a larger ecchymotic area There was no lymphangitis or ad nopa thy Blood cultures were positive for Streptobacillus moniliformis

Neither sulfathiazole intravenously and orally nor sulfadiazine by the same routes had any effect on the temperature course or bacteremia. Sulfonamides were given over 11 days during which

(9) Cl n 3 425 4 6 A g t 1944

time the patient showed no improvement and exhibited a down hill course with chills and fever Blood cultures remained positive

The patient was then given penicillin 0 000 units in 1 000 cc saline intravenously each morning and 15 000 units every three hours intramuscularly for three days Within two days the blood culture was negative for the first time and three more blood cultures on alternate days remained negative On this therapy the bite and an abscess which had appeared on the left leg during sulfonamide therapy showed healing Temperature was normal except for occasional slight elevations The amount of penicillin was then reduced approximately 50 per cent for five days but when fever recurred at this time dosage was elevated to the original 150 000 units daily Fever again subsided within three days After 0 days of penicillin therapy during which period the patient received 1 9?? 000 units the drug was discontinued A low grade fever persisted for five days thereafter then the temperature remained normal The patient was discharged after 50 days of hospitalization

[As a rule penicillin is ineffective in infections due to gram negative bacilli —Ed]

Treatment of Meningococcic Meningitis with Penicillin Manson Meads H William Harris, Bernardo A Samper and Maxwell Finland with the technical assistance of Clare Wilcox[1] (Harvard Univ) report on nine patients with meningococcic meningitis including five with meningococcemia treated with the calcium salt of penicillin intrathecally and intramuscularly Before treatment group I meningococcus was isolated in eight of the cases from the spinal fluid blood or nose and throat cultures In the remaining case a single dose of sulfadiazine had been given before admission and spinal fluid and pharyngeal cultures were negative Ages ranged from 14 to 58 years Duration of the acute illness before hospitalization ranged from one to seven days averaging three days Initial intraspinal doses consisted of 10 000–20 000 units of penicillin in 10 cc physiologic saline solution This was followed by 5 000–15 000 units intraspinally every 12 hours for two to five doses and every 24 hours after clinical and bacteriologic improvement was noted The number of intraspinal injections for each patient averaged about six and the total amount of pen

(1) N w E gl d J M d 31 509 16 O t 1 1944

icillin given intrathecally averaged 75 000 units Intra muscular therapy was given simultaneously Seven pa tients were given 15 000 units every three hours and two 10,000 units every three hours Duration of intramuscu lar therapy was 2½–6½ days In two cases, because of poor clinical response and persistence of abnormal bac teriologic and spinal fluid findings, penicillin was dis continued and sulfapyrazine given In one case, because of persistent positive throat cultures after one week of penicillin therapy sulfadiazine was given

On the basis of laboratory and clinical findings in this series and the accumulated results of sulfonamide ther apy, the authors conclude that the sulfonamides are the drug of choice in treatment of group I meningococcus meningitis and that penicillin may be effective in these cases in the doses used but the response is less favorable than with sulfonamides The clinical response to penicil lin is slower abnormal spinal fluid findings persist longer there may be recurrences, the meningococcus carrier state may persist the treatment is difficult and sulfonamides may have to be resorted to for cure Cal cium penicillin seems however to be quite effective against group I meningococcus bacteremia Strains of group I meningococcus vary markedly in their sensitiv ity to penicillin The strains studied here resembled the relatively re istant strains of Staphylococcus aureus and Streptococcus viridans

Human Ornithosis Treated with Penicillin F L Tur gasen (Manitowoc Wis) states that human ornithosis is probably more prevalent than commonly recognized failure to perform the complement fixation test may be responsible for the infrequency of diagnosis This disease may account for many cases of so called virus pneu monias Symptomatology resembles that of psittacosis gradual onset somewhat resembling typhoid of an atypi cal pneumonia with dry irritating unproductive cough Mortality is high sulfonamides have no effect Penicillin was curative as reported by Heilman and Herrell in

(2) J A M A 1 6 1150 1151 D 30 1944

mouse infection which had been experimentally produced

Man 43 owned homing pigeons several of which had died Seven days after he had cleaned the pigeon loft he complained of generalized aching headache fever and later abdominal d s comfort Temperature rose rapidly pulse rate was disproportion ately slow When hospitalized five days later he showed irrita bility slight impairment of mental co ordination and judgment photophobia a soft enlarged spleen moderate gaseous abdominal distention and an atypical consolidation of the left lower lobe po teriorly without râles X ray revealed a pneumonic infiltra tion centrally in the left lower lung Red blood cell count was 4 60 000 white count was 9,200 Two days later it was 11 100 with 78 per cent neutrophils 8 per cent lymphocytes 9 per cent monocytes 4 per cent eos nop1 ils and 1 unident fied mononuclear cell Blood cultures agglutination tests (typhoid paratyphoid undulant fever tularemia) and urine examination were negative The patient s serum fixed psittacosi antigen in a d lutio of 1 56 Ornithosis virus wa found in one of four pigeons x amined Penicill n 100 000 units in 10 cc sotonic solution of o hum chloride was injecte l nt amuscularly in divided dose daily for 7½ days In four days the temperature dropped to normal He was discharged the tenth day and in a month was fully recovered

Confluent Smallpox Treated with Penicillin M A Foulis[3] (Robroyston Auxiliary Hosp Millerston) re ports an unusual case

Seaman 38 unvaccinated presumably contracted smallpox in a North African port which did not develop until he was at sea Th disease began with chills headache pains in the limbs sore throat and general malaise An eruption appeared on the fore head When first seen in the hospital four days after onset of illness, the pat ent was afebrile and only moderately ill Tl e eruption was pronounced over the whole body On the fa t onsisted of large coalescing vesicles The scalp was markedly involved w thout as much confluence There were numerou v i cles on the mouth palate and gums especially where teeth had been remove l There we e lesions in the respiratory passages probably laryngiti and p ofuse papular and papulovesicular rash on the trunk On the rists and hands th eruption wa pra tically confluent part cularly over a s ar on the left leg The trunk had numerous le ions even on sites usually left free Tl e a eolae of the lesions were mo t ma ked on the h ad and n ck

A stormy illness was xpe ted ith a rash of su l p ofu ion nd penic llin was given intramus ularly since development of delirium might interfere with a ont nuou intramus ular lr y The pat ent was gi en 0 000 units of calcium penicillin the day

(3) B t M J 1 910 911 J 30 1945

after admission, when he again had fever Injections were re peated every four hours, and as the rash matured, every three hours Four days later it was apparent that the illness was not going to be as severe as thought a continuous intramuscular drip was therefore started with considerable subjective relief He re ceived 100 000 units daily for three days He was then conva lescent on the thirteenth day after onset of illness He had received a total of 800 000 units of penicillin At discharge there was no evidence of excess granulation tissue and pitting promised to be minimal It was interesting to note that most of the lesion on the trunk and limbs failed to increase in size after penicillin therapy was started and that most of them crusted, without pu tulation on or about the sixth day of appearance Desquamation was complete everywhere except on the palms and soles by the thirteenth day of eruption

It is not suggested that penicillin alone was responsible for the success in this case Alterations in immunity re sponse may change the predicted outcome of such an ill ness However penicillin achieved all that was expected of it whereas in comparable illnesses in previous out breaks intensive use of sulfonamides failed to prevent several fatalities

Penicillin in Experimental Spotted Fever Florence K Fitzpatrick[4] (Glenolden Pa) reports on use of pen icillin in guinea pigs infected with a virulent strain of spotted fever Large doses were injected intramuscularly every 4 hours beginning 48 hours after onset of fever Controls included untreated animals and others that re ceived one dose of spotted fever rabbit immune globulin All animals receiving penicillin died of the disease the treatment having no beneficial effect on any of the signs and symptoms characteristic of the strain of spotted fever such as loss of appetite and weight sustained high temperature and scrotal involvement Smears of spleen and lung at autopsy showed rickettsiae to be as numerous as in the untreated controls However, all animals treated with the globulin survived and progress of the disease was arrested Scrotal swelling subsided in about two days, whereas in most of the other controls and in the guinea pigs receiving penicillin the lesion progressed to petechial hemorrhages adhesions of the tunica vaginalis

(4) Science 10 96 97 July 7, 1945

and finally necrosis Studies of the plasma penicillin levels indicated that the dosage and time schedule used in the experiments should have been adequate to procure recovery if the agent had been effective The toxicity of penicillin for guinea pigs may have contributed to the failure

Pocky Mountain Spotted Fever Treatment with Penicillin P K Edmunds[5] (Cedar City Utah) reports a case

Boy 14 after numerous tick bites developed chills h gh fever headache backache and vomiting On hospitalization three days after onset he compla ned of midabdominal pain. Examination revealed pro tration del rium reddene l eyes and pharynx and a few papular le ions on the trunk and upper part of the extremities Temperature was 103 6 F pulse rate 1 0 per minute and respiratory rate 20 Bloo l count and urinalysis were uninformative Agglutination tests were positive for Rocky Mountain spotted fever and paratypho d B up to the third dilution The child had never been immunized for Rocky Mountain spotted fever but had been immunized for the typhoid group two months previously

A sulfonamide was given 2 Gm initially and 1 Gm. every four hours thereafter The next day the patient seemed generally worse Temperature ranged between 104 and 105 F The rash spread all over the body After 36 hours the sulfonamide was di continued and pen cill n begun 100 000 units being added to 500 c normal saline and given by intravenous drip throughout the day W thin two hours the tempe atu e dropped and the boy became rational Because of th dramati improvement penicillin was stoppe l when he had received about 0 000 units The temperature flared that n ght Next day the boy received the balance of the 100 000 un ts following which his temperature sub ded at first abruptly then gradually to normal in three days He was discharged and continued to improve at home

Edmunds hesitates to draw conclusions from one case but suggests that penicillin be given a more extensive trial He advocates administering at least 100 000 units without interruption

Weil s Disease Treated with Penicillin V Lloyd Hart[6] reports a case

Man 26 had pain in the r ght chest cou h and fever On hosp talization three days later auscultation revealed fine crepitation in both bases Rad ograph d closed opacity of th left

(5) Rocky M t n M J 41 910 911 D mbe 1944
(6) B t M J 2 7 0 Dec 1944

base Temperature was 102 F , pulse rate, 11? White blood cell count was 14 000 with neutrophils 96 per cent and lymphocytes 4 per cent Sulfamethazine was given without benefit On the sixth day the patient had conjunctivitis jaundice enlarged tender liver pale stools and bile pigments in the urine Icteric index was 55 A low fat high protein high carbohydrate diet, supplementary vitamins and a daily saline purge were prescribed The condition grew worse until the eighth day after which im provement was gradual Icteric index on the tenth day was 110 The patient s serum on the thirteenth day agglutinated Leptospira icterohaemorrhagiae 1 ?0 and on the eighteenth day 1 3 000 Leptospira were found in the urine between the twenty second and the thirty first day Beginning the thirtieth day the patient was given 15 000 units penicillin every four hours for three days or a total of 315 000 units Jaundice persisted till the forty second day

Penicillin may have cleared the urine of organisms but was administered too late to affect recovery Hart sug gests administration of penicillin before diagnosis can be established in any case with the typical white cell count in which Weil s disease is suspected

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MISCELLANEOUS CONDITIONS

Air Borne Infection Rationale and Means of Disin fection of Air Stuart Mudd[7] (Univ of Pennsylvania) reviews statistical records which show that respiratory disease is responsible for more than one third of the total number of person days lost to American industry by dis ability and that the number is steadily rising The prob lem is also serious in domestic life and during military training The air of enclosed spaces is at present con sidered the principal vehicle for dissemination of res piratory disease

Mudd reviews the many experimental trials with various agents to make the air safe for human occupancy by destroving the bacteria in it There are three inde pendent means of controlling dissemination of disease agents through the air by ultraviolet irradiation germi cidal vapors or dust suppressive measures The germi cidal vapors are those of hypochlorous acid and of pro

(7) Bull New York Acad Med 1 393-415 August, 19

pylene and triethylene glycol Each is capable under appropriate conditions of reducing significantly the incidence of respiratory infection Elaboration of the practical art of providing safe air supply is however not to be accomplished cheaply or through the efforts of a few people A specialty or specialties in sanitary engineering must be developed around air sanitation as has been done around water and milk sanitation Physicians air-conditioning specialists heating ventilating and illuminating engineers architects manufacturers of necessary equipment agencies of public health practice and industries which will benefit by reduction of industrial disability through respiratory disease must ultimately all contribute effort and money to solve the problem Considered in terms of cost in money and effort when applied on a national scale control of air borne infections seems to present a problem of immense proportions However compared with the cost of uncontrolled air *borne infection the money costs of preventive measures* shrink to rather trivial figures

Arthropod Borne Diseases may be divided into three types according to Ernest Carroll Faust[8] (New Orleans) (1) those directly caused by injection of venom or saliva as by scorpions etc or from invasion of skin or mucous membrane as by mange mites the chigoe and certain fly maggots (2) those mechanically transmitted by the house fly biting stable fly filth gnat and eye gnat and (3) those in which arthropods are essential biologic vectors It is with this last type that Faust is particularly concerned

Malaria transmitted by anopheles mosquitoes is wide spread throughout tropical and temperate climes but in the United States and among the troops overseas it is gradually being overcome

Yellow fever dengue and equine encephalomyelitis are virus infections transmitted by the house mosquito Aedes aegypti Yellow fever epidemic control has been achieved in Latin American cities by reducing the breed

(8) J P diat 25 63 583 Dec mb 1944

ing of aedes to 1 per cent of domiciles (in Brazil to 0 1 per cent) and by vaccination with a neurotropic strain of low virulence The vaccine is well tolerated but should not be administered during smallpox immunization or a virus disease Neglect of aedes mosquitoes in the United States in the last decades has created a potential menace but the U S Public Health Service is compaigning to cut breeding to 5 per cent of domiciles Dengue and equine encephalomyelitis can be similarly controlled

Sandfly fever transmitted by Phlebotomus papatasii has never been established in the Western hemisphere Clinically it resembles dengue though a rash is rare and the leukopenia more pronounced

The filarias threadlike worms are transmitted by mosquitoes or blood sucking flies Acanthocheilonema perstans and Mansonella ozzardi are relatively common but unimportant as they frequent the body cavities producing no pathology Loa loa migrates through subcutaneous tissues causing annoyance but not permanent tissue damage Onchocerca volvulus resides in subcutaneous tumors The embryo microfilaria however, migrates to the eye with grave consequences Infections with Wuchereria bancrofti and malayi are serious The adults invade the lymphatic system, provoking acute inflammatory reactions and fibrotic repair with obstruction of lymph flow, elephantiasis Many of several thousand exposed American troops have been infected There is no cure *Control depends on elimination of vectors*

The typhus fevers are caused by pleomorphic gram negative intracellular rickettsias which destroy the endothelial lining of small blood vessels producing hemorrhage thrombi and perivascular infiltration Vaccines prepared by the Cox or Castañeda technics from killed rickettsias are highly protective but specific to the species "Booster doses' must be given every one to two years Spotted fever Bullis fever and Q fever are tick borne and found in the United States Scrub typhus or tsutsugamushi disease, is transmitted by red mites or chiggers Control is by application of repellants Typhus

fever (etiologic agent Rickettsia prowazeki var prowazeki) is louse borne and disinfestation with DDT powder is a valuable emergency measure before vaccination can be accomplished Murine typhus (etiologic agent Rickettsia prowazeki var mooseri) is increasing in the southern United States 100 000 cases having occurred since 1926 It is enzootic in rats and transmitted by the rat flea (Xenopsylla cheopis) Trench fever is carried by body lice Rickettsia quintana may be the etiologic agent

Visceral leishmaniasis or kala azar is produced by Leishmania donovani cutaneous leishmaniasis by Leishmania tropica and mucocutaneous leishmaniasis by Leishmania braziliensis All three types are transmitted by the sandfly phlebotomus African sleeping sickness is caused by Trypanosoma gambiense and rhodesiense and Chagas disease by Trypanosoma cruzi Chagas disease exists in southwestern United States is transmitted by blood sucking cone nosed bugs (triatoma panstrongylus rhodnius etc) and may be demonstrated by complement fixation and xenodiagnosis Visceral leishmaniases and Chagas disease provoke a reticulo endotheliosis with splenomegaly hepatomegaly lymphatic hyperplasia and engorgement of bone marrow Severe constitutional reactions ensue Antimony pentavalent salts are specific for the leishmaniases excepting Sudanese and Kenya kala azar in which diamidines are better Trypanosoma gambiense and rhodesiense infections respond to tryparsamide and germanin The latter is used prophylactically There is no treatment for Chagas disease Permanent immunization is possible against Leishmania tropica

Carrión s disease or verruca peruana (vector sand fly) is limited to Peru Ecuador and Colombia

Plague (etiologic agent Pasteurella pestis) is enzootic in United States rats and transmitted by the rat flea Vaccines (Haffkine killed organisms in India and Otten attenuated living organisms in Java) have proved fairly effective Immune serum and sulfonamides have proved of value

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Summary of Data in Cases of Chronic Monarticular Arthritis

Case	Age Yr	Sex	Joint Involved	Duration of Symptoms	Presumptive Diagnosis	Course	Time Followed Yr	Final Diagnosis
1	[illegible]	M	Right knee	1 mo	Rheumatoid arthritis	Increasing disability	5	Tuberculosis
[illegible]	[illegible]	F	Left hip	18 mo	Tuberculosis	Recovery	[illegible]	Chronic sprain
[illegible]	11	M	Right knee	[illegible]	Tuberculosis	Other joints involved	4	Rheumatoid arthritis
4	11	M	Left knee	[illegible]	Tuberculosis	Increasing disability	[illegible]	Tuberculosis
[illegible]	[illegible]	F	Left knee	8 yr	Tuberculosis	Other joints involved	4	Rheumatoid arthritis
[illegible]	18	F	Left hip	[illegible]	Acute infection	Eventual ankylosis	3	Acute infectious arthritis
7	[illegible]	F	Left ankle	18 mo	Tuberculosis	Increasing disability	2	Tuberculosis
8	[illegible]	F	Right shoulder	6 mo	Rheumatoid arthritis	Rapid recovery	6	Hysteria
9	31	F	Right knee	6 mo	Acute infection	Improvement	3	Gonococcic arthritis
10	34	F	Left knee	10 mo	Acute infection	Ankylosis	4	Acute infectious arthritis
11	[illegible]	M	Left knee	7 mo	Tuberculosis	Recovery	7	Rheumatoid arthritis
[illegible]	4	M	Left hip	5 mo	Tuberculosis	Died	1	Sarcoma
[illegible]	46	F	Right elbow	[illegible]	Rheumatoid arthritis	Slow progression	2	Tuberculosis
14	61	F	Right knee	[illegible]	Osteo arthritis	Slow progression		Tuberculosis

Tularemia is enzootic in United States wild mammals and birds and may be spread by direct contact or through ticks fleas, mosquitoes and deer and biting stable flies

Relapsing fevers are epidemic and louse borne, and endemic and tick borne Both forms have occurred in the United States The latter is still extensive In both, the spirochetes reside in the viscera except during paroxysms, when they swarm through the peripheral blood Neoarsphenamine administered at the beginning of a paroxysm is curative

Faust emphasizes the importance of vaccination in arthropod borne diseases for which vaccines exist, particularly for children in endemic areas, temporary expedients such as disinfestation with DDT powder, use of pyrethrum sprays pyrethrum freon pressure bomb and repellent mixtures of dimethylphthalate, indalone and Rutgers 612 and above all vigorous measures against vectors and rodents So long as citizens are disinterested in eradication of Aedes aegypti yellow fever and dengue will be a menace so long as rats abound there will be murine typhus and the possibility of plague

Chronic Monarticular Arthritis John G Kuhns[9] (Robert Breck Brigham Hosp Boston) states that diagnosis in this condition is often difficult because of vague and confusing symptoms and signs most of them suggesting only chronic inflammation It is frequently necessary to wait for further signs to determine the etiology Until correct diagnosis is made treatment must be symptomatic and directed to relief of symptoms and prevention of further disability Kuhns observed 15 cases among 2 268 of chronic arthritis in which diagnosis could be made only after prolonged observation However in most cases of acute monarticular arthritis the cause of inflammation in the joints is evident and is usually a preceding injury or an acute infection In these cases recovery is usual and when healing is delayed the subsequent course of the disease generally leaves no doubt concerning diagnosis

(9) New England J Med 3 1 8 132 F b 1 1945

deleterious effect on the sexual functions Swollen lymph nodes rubbery in consistency and remaining discrete appear in the inguinal cervical axillary or epitrochlear regions Lymphangitis which may develop in arms neck or thighs *proceeds in a retrograde or centrifugal direction* in association with a red streak under which the enlarged vessel may be palpable Sometimes circumscribed localized areas of swelling occur in arms or legs which are dull red tense and edematous Urticaria or other skin changes are rarely seen Conjunctivitis may be present Pleural friction rubs have been heard Moderate leukocytosis was present in about one third of the cases and eosinophilia in about two thirds owing to the frequent presence of intestinal parasites The urine shows no significant changes Repeated or prolonged *attacks occasionally leave enlargements or thickenings* usually of lymph nodes or genitalia especially the spermatic cord which are rarely marked but are detectable in the intervals between acute attacks A concomitant bacterial infection is not necessarily present The clinical manifestations have no relation to the presence of microfilarias in the blood

Late changes are associated with permanent changes in the tissue lymph node enlargement and elephantiasis Again there is no relation to presence of microfilarias in the blood Elephantiasis is not however a necessary *consequence of infection heavily infected populations* may show it in only 5 per cent or less of their numbers

Diagnosis should not be made without demonstration of microfilarias or adult worms or indicative history and clinical findings Treatment consists of bed rest in the acute attack with cold or hot compresses over local inflamed areas and elevation of swollen parts Operations should be postponed unless absolutely necessary as emergencies There is no specific chemotherapeutic agent for the condition Sulfadiazine may be given if secondary infection with susceptible bacteria exists Main *emphasis should be placed on reassurance* of the patient to overcome the great fear in the minds of most men

In 14 of the 15 cases other conditions which had to be considered in diagnosis were rheumatoid arthritis and articular tuberculosis Data concerning these cases are shown in the table

The experience with these 14 cases indicates the caution with which a diagnosis of chronic monarticular arthritis must be made, this is especially true in atypical chronic monarticular arthritis Deformity can be prevented by traction plaster casts or other appropriate apparatus Surgical measures should not be carried out until diagnosis is definitely established Attempts should be made to promote strength and motion in the joint as the symptoms subside

Filariasis (Wuchereria) *A bulletin issued by the* War Department[2] enumerates all known factors concerning this condition with special emphasis on the early stages These early symptoms and signs were noted particularly on the islands of the southern part of the Central Pacific region where the nonperiodic variety of Wuchereria bancrofti is found

The manifestations occur in a series of acute attacks lasting five to six days or for several weeks Recurrences are not periodic Strenuous exercise or hard work may precipitate attacks In the time between attacks patients appear normally healthy Symptoms of acute attacks are lack of energy and stamina constant fatigue anorexia nausea headache vertigo drowsiness blurring of vision photophobia and muscle spasm Pain is common but usually light occurring in chest lower abdomen and muscles in association with local swellings and lymphangitis Fever chills and prostration are unusual except in mild degree Neurotic symptoms are frequent and mental depression may be severe Physical signs are mostly those of enlarged lymph nodes other localized swellings and lymphangitis Involvement of the genitalia is most frequent, with retrograde funiculitis epididymitis orchitis varicocele and edema of scrotal skin No evidence has been found that early filariasis has any

(2) War Med 7 377 384 J n 1945

the most frequent site of entrance The large number of patients with ulcerated lesions of the mouth pharynx and gastro-intestinal tract bears out this conclusion The many cases of lesions of the nose pharynx, larynx and lungs may also be evidence pointing to the respiratory tract as the portal of entry A smaller group of cases suggests entrance through the skin The fungus is unknown in its vegetative form in nature but the parasitic form has been identified in the dog and a similar organism apparently the same has been found in mice rats and ferrets

Treatment is still experimental Certain antimony preparations and a new diamidine preparation are promising In differential diagnosis tuberculosis Hodgkin s disease aleukemic leukemia and malignant neoplasms must be considered Diagnosis has been made before death by histologic examination of biopsy material Blood cultures cultures of biopsy material and smears or scrapings from superficial lesions have been successful in several cases Least successful although with certain outstanding exceptions have been examination of blood smears and of sternal marrow However the two methods should not be abandoned

Summary of Studies on Immunity in Mumps John F Enders[4] (Harvard Univ) points out that induction into the army of millions of young men who may be susceptible to mumps made this condition a problem Incidence of mumps in the armed forces has been relatively low compared with 1917 but it is not negligible Experimental investigations determined that the complement fixation test is a particularly valuable laboratory method of diagnosis in cases in which infection with the virus of mumps is suspected but clinical signs are inconclusive e g when involvement of the salivary glands is absent or questionable Both the complement fixation test and the skin test for dermal hypersensitivity seem reliable if not absolutely accurate means of finding most individuals who are immune or potentially

(4) T & St d C ll Ph Ph l d lph 13 23 36 Ap l 1945

concerning transmission and the development of ele phantiasis After the acute attacks are over, the patients should be given a reconditioning program with main emphasis on careful supervision and proper psychologic management and morale building Prevention of filari asis depends primarily on segregation of troops at a safe distance from infected native populations control of mosquito vectors and individual protection from mosquito bites

Histoplasmosis in Man Robert J Parsons and C J D Zarafonetis[3] (Univ of Michigan) present a report of 7 cases and a review of 71, including those from the literature and a few as yet unpublished Since 1936 incidence of histoplasmosis has suddenly increased, pos sibly because of better recognition of the condition The disease is no longer tropical but appears in temperate as well as subtropical regions It occurs more frequently in males than in females and affects persons of all ages although the greatest incidence has occurred during the first fifth sixth and seventh decades The commonest signs and symptoms in order of decreasing frequency are fever hypochromic anemia hepatomegaly spleno megaly and lymphadenopathy Anorexia and loss of weight are common Ulceration of the oral mucosa particularly the tongue various types of cutaneous lesions and ulceration of the pharynx and larynx occur frequently

The yeastlike or parasitic form of the fungus charac teristically is found in cells of the large macrophage or reticulo endothelial system At autopsy the organs are found to be involved in the following order of frequency spleen liver visceral lymph nodes lungs bone marrow oral mucosa adrenals gastro intestinal tract, peripheral lymph nodes kidneys and larynx Vegetative endocarditis occurred three times Any or all of the remaining organs may be involved The portal of entry of the fungus is not known although more and more evidence is accumulating pointing to the mouth as

(3) Arch Int Med 75 1 3 January 1945

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(4) T & St d C B Ph Phil 1lph 13 336 Ap 1 1945

susceptible The skin test is simpler although further experimentation is needed to fix its limitations This test was performed by injecting intradermally 0 1 cc of *heated and diluted* virus suspension *It* was considered positive if a zone of erythema developed about the site of inoculation with slight induration near the center after 24–48 hours

Induction of active or passive immunity has not been successful results of experiments on the effect of pro phylactic vaccination with *formolized suspensions of* monkey virus are however encouraging

Septicemia and Purpura with Adrenal Hemorrhage in the Adult H B Thomas (*York Pa*) *and* C D Leip hart[5] (New York City) discuss the role of the adrenal gland in production of the Waterhouse Friderichsen syndrome This syndrome of bleeding into the skin and other organs including the adrenals in the presence of *severe septicemia is being recognized more frequently* The meningococcus seems definitely established as the most frequent invading organism although other organ isms have been isolated

The hemorrhagic destructive lesion of the adrenals was long considered the cause of the dramatic death, however *animal experimentation and reports of recov* eries or of autopsies on patients in whom there was a unilateral cortical lesion or no adrenal involvement disprove this theory Adrenalectomized dogs lose appe tite and become weak and listless with vomiting diar rhea pronounced depression feeble pulse and low blood pressure and metabolic rate The same symptoms appear in patients with the Waterhouse Friderichsen syndrome with one important *difference—the time required for* them to appear The period between onset of symptoms and death is measured in hours and seldom exceeds two days average survival in adrenalectomized dogs is seven days Onset of changes in the experimental animal is slow and insidious, the subject becoming apathetic and sluggish weak in the hindlegs, then lying prostrate

(5) J A M A 1 5 884 890 J ly 9 1944

refusing food and often vomiting Muscular twitchings and frank convulsions develop respirations become slow and labored and eventually cease Identical changes occur rapidly in man and are complicated with profound overwhelming infection that has produced sepsis and hemorrhagic phenomena

Clinical features are identical in fatal and nonfatal cases That even mild bilateral lesions of the cortex could produce such profound disturbances of the individual and still regress completely is difficult to conceive While one eleventh to one fourth of one adrenal cortex can maintain life in the experimental animal it is not reasonable to suppose that rapid destruction of the major portion of the cortex will produce the syndrome rapidly because that is not the case in complete adrenalectomy Regeneration of the glands can likewise be eliminated Rarely does any process resembling regeneration accompany disease of the organ itself

Production of the Waterhouse Friderichsen syndrome is undoubtedly initiated by a bacterial invasion of the blood stream Meningococcic meningitis usually shows a stage of dispersion in the blood stream after a period of local infection in the upper respiratory tract The wide hemorrhagic phenomena of the skin adrenals and many other tissues have been thought to result from direct action of the bacteria or their toxins on the walls of the capillaries

Removal of the adrenal medulla produces no definite change in physiology of the animal many observers have noted that surgical removal of both adrenal cortexes will not produce symptoms of insufficiency for at least several days The rapidity with which symptoms appear in an apparently healthy individual makes it difficult to ascribe their origin to adrenal insufficiency However important the adrenal glands are to the body economy they are just one of the tissues that manifest capillary weakness If death did not supervene so quickly loss of the cortical hormone would present a serious complication in a few days

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(5) J A M A 1 5 884 890 July 9 1944

childhood If necessary legislative measures must be established to prevent epidemic outbreaks and to reduce the mortality of the endemic disease in thickly populated areas like Bombay

Further effects of chemotherapy were reduction of incidence of septic complications like ulcers abscesses otitis media corneal ulcers bedsores etc as well as the pulmonary complications of bronchitis and bronchopneumonia Previous vaccination helped to reduce these complications further Incidence duration and severity of secondary pyrexia also were reduced by chemotherapy again more so in the vaccinated patients The scabs in patients receiving sulfanilamide became papery and superficial and fell off leaving a clean healthy scar without much deformity This effect was especially marked in vaccinated patients

Typing of Staphylococci by the Bacteriophage Method G S Wilson and J D Atkinson[7] (Oxford Univ) examined 1 340 strains of Staphylococcus aureus most of which were derived from the nose hands skin lesions breast abscesses wounds or burns of patients with *staphylococcic infections or from suspected nasal* or skin carriers A few were isolated from food thought to be responsible for poisoning of the toxin type or from the vomit or feces of persons with food poisoning Of the total 46 were used for obtaining strains of bacteriophage by Fisk s cross culture method Twenty nine of the 46 strains showed evidence of lysis 25 of them were latent carriers of phage and 7 different strains of bacteriophage were obtained from them Eleven further phage strains were prepared by growing one of the original phages in the presence of a later strain a variant of the phage being developed

Of 460 cultures 278 were typed 104 were acted on by phage but did not fall clearly into any of the types so far defined and 78 proved insusceptible to all the lytic filtrates used Figure 1 shows the method by which the different types of staphylococci were recog

(7) L t 1 647 648 M y 26 194

From observation of two cases and study of the literature, the authors believe that death occurs from overwhelming septicemia with superinduced state of shock The concomitant massive adrenal hemorrhage excites interest because it has long been known that loss of cortical hormone produces fatal disorders of systemic functions that are identical in most features with those of surgical or traumatic shock However the illness is too brief to be attributed to the loss of this hormone

Clinical evidence that adrenal hemorrhage plays little or no part in the rapid death of the patient is furnished by Williams with autopsy findings on 17 children with fulminating meningococcic septicemia Classic clinical features were identical in all cases so also were the autopsy findings except that only nine patients presented bilateral adrenal hemorrhage

Sulfanilamide in Smallpox S G Vengsarker and J V Rangnekar[6] (Bombay) report the results of *chemotherapy in 312 patients with smallpox as compared* with those of routine symptomatic treatment in 236 patients Sulfanilamide attenuated the virulence of the virus as shown by reduction of toxemia abortion of eruptions and lowered mortality rate particularly in the more virulent type of the disease *Previous* vaccination also attenuated the virulence of the virus Chemotherapy especially shortened and modified the course of the disease by abortion of the rash when the drug was given early in the papular stage this effect was again more pronounced in the vaccinated patients The discrete variety of the disease with low mortality rates was found much more frequently in the vaccinated than in the unvaccinated patients

The gradual waning of immunity after primary vaccination results in a maximal incidence of the disease in adults between 16 and 40 years A child should be revaccinated when entering school and again when finally leaving school to reinforce the original vaccination immunity in infancy *and the revaccination in*

(6) J I d M A 13 13219 M y 1944

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nized As shown, there are 21 types or subtypes Included in types 1 2 and 3 were strains of staphylococci acted on by more than one test filtrate in the series, even though as with 1B and 3B the action of only one

Confluent lysis = + semiconfluent lysis = ± lesser degrees of lysis or no lysis = −

Phage type of occus	Bacteriophage filtrates																					
	J/ 84	3/211	31 14	6/3	7/4	42/1163	47/38	47/1163	29/33	31/18	32/144	3/284	38/1339	4 A/1307	44/18	44/3 3	44/ 81	47/981	44/1163	51/14	5 /144	52/925
1A	+	−	+																			
1B	−	+	−																			
1C	±	+	+																			
2A				+	−	+	+	+														
2B				±	+	+	+	+														
2C				−	−	+	−	+														
2D				−	−	−	+	+														
3A									+	+	−											
3B									−	+	−											
3C									−	+	+											
4												+										
5													+									
6														+								
7															+							
8																+						
9																	+					
10																		+				
11																			+			
12																				+		
13																					+	
14																						+

The bacteriophage filtrates are designated according to the strain from which the phage was originally derived (first number) and the strain on which it was propagated (second number)

Figure 1

filtrate was recorded Strains belonging to types 4–14 however were lysed completely by a single filtrate only when used in the test dilution although they may prove susceptible to fresh strains of bacteriophage still to be isolated Analysis of frequency distribution of the 21 types showed that apart from types 12 and 14 no type comprised more than 10 per cent of the whole

The authors report some outbreaks of epidemics in which their method of phage typing proved useful These included two outbreaks of food poisoning and two of pemphigus in maternity homes

GENERAL CONSIDERATIONS

Mode of Action of Chemotherapeutic Agents According to Rene J Dubos[8] (Rockefeller Inst) chemotherapeutic agents may act by stimulating normal defense mechanisms of the body by decreasing the noxious effect of the invading parasite or by killing or inhibiting the infectious agent In practice successful chemotherapy has resulted only from inhibiting bacterial growth

The receptor theory formulated by Ehrlich is that the antimicrobial agent combines with certain chemically reactive cellular structures receptors Susceptible cells possess numerous receptors essential to their metabolic functions such as reduced thiol groups Evidence indicates that arsenicals and possibly mercurials owe their physiologic activity to their affinity for these Acid base reactions are important with the basic antibacterial dyes (triphenylmethane and acridine compounds) the basic ions form feebly ionized compounds with the acidic groups of bacteria Conversely with the acid dyes (acid fuchsin) the acidic ions react with the basic groups of bacteria resulting in the ordinary type of double decomposition With the synthetic soaps (anionic and cationic detergents) there is probably an acid base or base acid union The disinfectant property of the phenolic compounds may be due to the combination of the hydroxyl group (acidic) with the amino groups of bacteria

The lock and key relationship theory introduced by Fisher postulates that the structural configuration of the reacting molecules conditions the reaction between enzyme and substrate This accounts for the specificity of many biologic phenomena particularly the phenomena of specific inhibition the blocking of enzymatic reaction by substances which having a molecular structure similar to the normal substrate react and combine

(8) B U N w Y k A d M d 21 736 J n ry 194

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Phage type of coccus	Bacteriophage filtrates: 3/ 84	3/ 11	52/145	6/3	7/4	42/1163	47/36	47/1163	9 33	31/18	52/144	3 84	3B/1339	42A/1307	44/18	44/373	44/761	47/987	19/1163	51/145	52/145	52/025
1A	+	−	+																			
1B	−	+	−																			
1C	±	+	+																			
2A				+	−	+	+	+														
2B				±	+	+	+	+														
C				−	−	+	−	+														
2D				−	−	−	+	+														
3A									+	+	−											
3B									−	+	−											
3C									−	+	+											
4												+										
5													+									
6														+								
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by adding an excess of the normal carboxylic metabolite

Antiseptics behave as gross protoplasmic poisons Chemotherapeutic agents selectively affect some specific metabolic step sulfonamides possibly a synthetic anabolic process penicillin cellular division etc Inhibition of bacterial growth may result from processes other than those of cellular nutrition and respiration generally studied This is important in in vitro screening of antimicrobial agents Had criteria been limited to such factors as oxygen uptake there would be no sulfonamides and penicillin New assay technics and study of anabolic metabolism growth and cellular division are needed. Broader knowledge of cellular metabolism may bring about better understanding of the intimate mechanism of drug action

Synergistic Action between Sulfonamides and Certain Dyes against Gram Negative Bacteria F S Thatcher[9] (McGill Univ) reports experiments with sulfonamides and eH indicator dyes to determine their activity against both Staphylococcus aureus and Escherichia coli A pronounced synergistic effect became noticeable The sulfonamides which normally have little if any effect on gram negative bacteria would in the presence of 1 28 000 methylene or brilliant cresyl blue completely inactivate 10 000 000 cells of a 24 hour culture of Escherichia coli in 10 cc of nutrient broth buffered at pH 6 8 and containing a final concentration of 1 14 000 sulfapyridine sulfathiazole or sodium sulfathiazole

Clinical studies indicate a promising therapeutic value for the combination of sulfathiazole and methylene blue in treatment of chronic genito urinary infections caused by gram negative bacteria

Hemorrhagic Complications with Death Probably from Salicylate Therapy C T Ashworth and J F McKemie[1] (Dallas Tex) report two cases

CASE 1 —Girl 0 was hospital ed w th swelling and pain of left ankle elbow and wrist diagnosed a a ute rheumat c fever

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with the enzyme but are not transformed by it The competitive inhibition theory probably explains why p aminobenzoic acid neutralizes the bacteriostatic action of the sulfonamides Sulfanilamide and p aminobenzoic acid, an essential growth factor, are closely related structurally If the sulfonamides are effective by replacing p aminobenzoic acid in an essential metabolic reaction surplus of p aminobenzoic acid would prohibit the replacement

Whether results are bacteriostatic or bactericidal often depends on quantitative rather than qualitative elements Bactericidal effectiveness is enhanced by the formation of nondissociable complexes between the agent and bacterium Factors influencing the formation are surface activity and molecular weight of the agent and nature of the bacterium Organisms differ in strength and stability of chemical reaction and also in susceptibility *to secondary irreversible alterations and therefore* death Agents that are only bacteriostatic for streptococci are bactericidal to pneumococci which undergo autolysis more readily Heat favors irreversible change probably because catabolic reactions are increased and there is more rapid exhaustion of reserve substance Dissociable chemical complexes formed between agent and bacterium may be reversed by modification of acid base conditions removal of antibacterial agent or addition of substances with affinity for the agent Thus bacteria killed by mercury will multiply after treatment with soluble reduced sulfur compounds (hydrogen sulfide, glutathione cysteine etc) which exhibit affinity for mercury

The theory of competitive inhibition is indirectly supported by synthetic production of antibacterial compounds Pyridine 3 sulfonic acid amino-sulfonic acids and thiopanic acid (pantoyltaurine) bear the same relationship to nicotinic acid aminocarboxylic acids and pantothenic acid that sulfanilamide bears to p amino benzoic acid All these sulfonic analogues inhibit bacterial growth and in all cases the inhibition is reversed

hypoprothrombinemia Link and his co workers in experiments on rats demonstrated hypoprothrombinemia and pointed out the similarity between the salicylate radical and dicumarol a strong hypoprothrombinemic agent Vitamin K prevents this hypoprothrombinemia and therefore is strongly indicated whenever large doses of salicylates are given

[It is quite clear from this report that the recently recommended huge doses of salicylates are dangerous enough to be avoided —Ed]

Streptomycin in Treatment of Experimental Infections with Micro Organisms of Friedlander Group (Klebsiella) F R Heilman reports in vitro tests with nine different strains of organisms of the Friedlander group which indicate that growth of the organisms is inhibited by streptomycin In vivo tests indicated a marked protective effect of streptomycin for mice infected by intra abdominal inoculation with three different strains of the organism Of 69 mice inoculated with 1 000–10 000 times the lethal dose of the organism intra abdominally and treated with 185–500 units of streptomycin daily in divided doses for two or three days 62 (90 per cent) survived of 49 mice which did not receive treatment all died When mice were infected by the intranasal route more prolonged treatment was necessary to obtain protection Of 10 such mice treated for three days with 500 units of the drug daily only 2 survived and all of 10 untreated controls died Of 15 mice treated for seven days with the same dose of the drug per day 13 survived all of the 15 untreated controls died

These results suggest that streptomycin may be used in treatment of the various infections caused by organisms of the Friedlander group in man These organisms occasionally cause a severe type of pneumonia they have been found in the pus in many suppurative conditions of various parts of the body in sputum of patients with chronic bronchitis and in nasal mucous membrane of patients with ozena and rhinoscleroma Herrell used

( ) P St ff M t M y Cl 0 33 39 F b 7 1945

Ten Gm sodium salicylate in 1 000 cc isotonic solution of sodium chloride was given intravenously 30 drops per minute on two successive days, with improvement in the joints The same amount of sodium salicylate was then given orally for five days The second day of oral administration tinnitus developed swelling and pain completely disappeared The fifth day she became irrational and paranoid and began having hysterical outbursts and periods of tachypnea and hyperpnea followed by sweating and cyanosis Temperature rose to 102 F and the following day to 106 4 F Blood pressure fell to 80/40 There were a flaccid paralysis with absent deep reflexes and normal spinal fluid Urine showed specific gravity 1 025 325 mg albumin 4 plus acetone 5 pus cells and 300 red cells per high power field and many finely and coarsely granular casts Blood examination showed 3 650 000 red cells 9 5 Gm hemoglobin and 11 050 white cells with 9 per cent band cells 77 per cent segmental cells 6 per cent lymphocytes and 8 per cent mononuclears Blood urea nitrogen was 45 mg carbon dioxide-combining power 46 volumes per cent The patient died eight days after admission

Autopsy revealed petechial hemorrhages throughout the brain and in the peritoneum mesentery retroperitoneal tissues pericardium pancrea large and small intestine skin and spinal cord diffuse hemorrhages in the lung small subdural hemorrhage hepatic degeneration, and early bronchopneumonia

Case 2 —Negro boy aged 4 months was treated for a cold with one half an aspirin tablet (0 17 Gm) every four hours for four doses The third day he was hospitalized because of deep and rapid respiration Examination revealed mildly injected ear drums generally reddened throat harsh breath sounds depressed reflexes craniotabes and beading of the costochondral junction. Urine showed 4 plus acetone Because of the apparent *acidosis 2?0 cc lactate isotonic solution of three chlorides* was given intravenously and 250 cc subcutaneously Temperature rose to 106 F following which the infant received two doses of one half an aspirin tablet cool sponges and sulfathiazole 0 5 Gm initially and 0 25 Gm every four hours Convulsions developed and were controlled by 0 ?3 Gm sodium phenobarbital Death occurred 12 hours after admission

Autopsy showed acute cerebral hyperemia with pinpoint hemorrhages in hypothalamus medulla and cerebellum alveolar hemorrhages and focal atelecta is in the right lung small epicardial petechial hemorrhage acute hyperemia in the adrenal medulla kidneys and intestine degeneration of the liver aspiration of stomach contents and rickets

The recent trend toward intensive salicylate therapy usually considered relatively safe makes the occurrence of fatalities noteworthy The hemorrhagic pathologic changes may be the result of capillary damage and

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( ) P St ff Meet M y Cl n 20 33 39 F b 7 1945

streptomycin in the treatment of two patients with infections of the respiratory tract whose sputum had persistently yielded klebsiella, in both cases the organism promptly disappeared

Streptomycin in Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil s Disease) F R Heilman[3] reports that streptomycin exerted a considerable protective effect against experimental infections with Borrelia novyi and Leptospira icterohaemorrhagiae Previous experiments concerning the effect of penicillin on relapsing fever in mice indicate that streptomycin is relatively less effective than penicillin Further experiments are needed to compare the effect of smaller doses of streptomycin and penicillin on experimental relapsing fever

Penicillin was found to be more effective than streptomycin in experimental leptospirosis in hamsters When streptomycin was given in divided doses at the rate of 800 units per day for 10 days beginning 17 hours after infection however hamsters were effectively protected against at least 1 000 lethal doses of the spirochete It is possible that streptomycin may be used effectively as an adjunct to penicillin therapy in treatment of spirochetal infections in man

Nutrition of the Host and Natural Resistance to Infection Howard A Schneider and Leslie T Webster[4] (*Rockefeller Inst*) report on the effect of diet on the response of several genotypes of Mus musculus to Salmonella enteritidis infection Their experiments showed that a diet of whole wheat and whole dried milk promoted a higher survival rate among W Swiss mice subjected to Salmonella enteritidis infection than a "synthetic" diet This synthetic diet contained all known essentials of nutrition in as pure a state as possible All known vitamins available in pure form were included at levels at least 10 times the known minimal requirements

(3) *Proc Staff Meet Mayo Cl* 20 169 176 M y 30 1945
(4) J Exper Med 81 354 384 Ap 1 1945

Further investigation showed that this ability of the diet to condition natural resistance depends on the genetic constitution of the mice used It was found in W Swiss mice a strain only moderately inbred and retaining a degree of genetic variability but not in three other strains of highly inbred mice which were used because they differed predictably from one another in natural resistance

Addition of either whole wheat or dried milk to the synthetic diet showed that the nutritional factors which are responsible for the higher resistance to infection are contained in the whole wheat not the dried milk One of the responsible factors may possibly be folic acid which occurs in wheat in at least five times the amount found in dried whole milk However potatoes also contain a large amount of folic acid about three times as much as whole wheat yet mice on a potato diet have not shown much resistance Further experiments with folic acid and another newer vitamin biotin are needed

Shock in Acute Infections H D Warren V G Balboni F T Rogliano and A Feder (M C A U S) report the occurrence of shock in three cases of acute infection and point out the importance of preventing shock as a cause of death The three infections were scarlet fever septicemia and primary atypical pneumonia Certain similarities in temperature pulse respiration and blood pressure behavior were noted in these cases and are reported as a warning of impending events There was an abrupt rise in temperature to a high level shortly preceding the overwhelming spread of the infection This was followed by an equally abrupt fall although pulse and respirations did not correspondingly drop Oliguria was present during the period of hypotension Each patient had been examined before onset of shock and clinically presented evidence of an essentially normal cardiovascular system and appeared to have good fluid balance

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In these three cases shock probably arose from sudden invasion of the vascular system by bacteria or bacterial toxins or both with paralysis and dilatation of the capillary bed followed by pooling of blood in the dilated capillaries with a concomitant reduction in the venous return to the heart and in the cardiac output In the case of scarlet fever of severe toxicity, a true bacterial exotoxin was probably absorbed into the blood stream Temperature and some of the toxic manifestations were controlled by intravenous administration of pooled convalescent scarlet fever serum However the tone of the vascular system did not return until the fourth day and during that time intravenous administration of fluid and plasma was necessary to maintain blood pressure at a critical level The disparity between the circulating blood volume and the size of the vascular bed was further aggravated by loss of fluid through vomiting and diarrhea The second case was one of fulminating meningococcemia with massive invasion of the blood stream by bacteria and bacterial products By means of intravenous administration of fluid and plasma the circulating blood volume and critical level of the blood pressure were maintained until the infection could be controlled by sulfadiazine Many of these patients die in severe shock before the infection can be controlled by chemotherapy The third case was one of type III pneumococcus pneumonia Although blood cultures failed to demonstrate a septicemia the severe state of peripheral vascular collapse was probably due to invasion of the blood stream both by bacteria and by bacterial products Again the circulating blood volume was maintained by intravenous administration of plasma and fluids, while the infection was treated with sulfadiazine and type III antiserum

These three cases show that institution of specific measures to combat the infection is of primary importance since they are directed at the cause of the state of shock Adequate circulating blood volume must be maintained to overcome secondary shock while specific

measures are instituted to control the infection Caution is required in certain types of acute pneumonia particularly interstitial pneumonia frequently seen in young children since here overly enthusiastic use of procedures designed to restore inadequate circulating blood volume may result in increase in exudation in the lungs and thereby harm the patient

Some Recent Advances in Bacteriology and Virus Research with Special Reference to Electron Microscopy are discussed by Gregory Shwartzman[6] Primary virus lesions are essentially proliferative and degenerative inflammatory changes presumably are due to supervening bacterial action As shown by Gratia and by Shwartzman and his associates intravenous injection of a potent bacterial filtrate following intradermal injection of vaccinia virus converts a mild erythematous vaccinal lesion into a severe hemorrhagic and necrotic site surrounded by extensive inflammation This parallels the clinical observation in hemorrhagic smallpox which is almost invariably associated with hemolytic streptococcus bacteremia

Strict neurotropism implying that the virus grows and multiplies along the nerve trunk and is not found in the blood is exemplified by the virus of anterior poliomyelitis An example of pantropism in which the agent is also discovered in the blood is equine encephalitis of the Western and Eastern types recently established also as a natural disease in man A study by *Shwartzman of the mode of transfer of the pantropic* virus through the blood in experimental lymphocytic choriomeningitis suggested that this transfer is accomplished by means of erythrocytes

The consensus is that the intracytoplasmic inclusions may be identical or closely related to the viruses However the relation of the many intranuclear inclusions to the virus is dubious

Recent methods of studying the size of virus particles are based on ultrafiltration through collodion membranes

(6) J Mt S H p 11 137 158 S pt O t 1944

(Elford) velocity of sedimentation of particles (Svedberg) electrophoreses (Tiselius) and electron microscopy Shwartzman studied the virus of lymphocytic choriomeningitis by means of electron microscopy, using brains of infected animals and spinal fluid from a patient with lymphocytic choriomeningitis Three forms of well defined morphology, were found an elliptic body of high density an elliptic body of high density to which was attached a long filament and giant forms Clumping by immune guinea pig anti-lymphocytic choriomeningitis serum and human convalescent serum suggested that these bodies may be closely related to the virus of lymphocytic choriomeningitis

Conception *of the nature of viruses may be greatly* aided by examination of the so called pleuropneumonia like micro organisms The pleuropneumonia organism was *first discovered in a severe disease in cattle in 1898* a similar strain causes agalactia in sheep In certain phases the micro organism is closely related to viruses *it is filtrable invisible under the light microscope,* and parasitic for the cells of the host In other stages it bears all the characteristics of a true bacterium and *in some forms approaches protozoa in form and mode* of reproduction It therefore may be broadly considered as a connecting link between the three species Shwartzman *believes his recent recovery of this pleuropneumonia* like organism from the blood of a patient is the first instance recorded in man The micro organism was *believed responsible for fatal subacute endocarditis in* the patient who had a history of rheumatic heart disease Obviously the agent had been present in the blood for a long time, *since a strong precipitation reaction was* obtained with the patient s serum against an antigen prepared from the micro organism

Effect of X Ray Irradiation on Bacterial Toxemia in Rabbits was studied by J Dewey Bisgard Howard B Hunt and R Hugh Dickinson[7] (Omaha) In a previous experiment rabbits *receiving 100 r over the abdomen*

(7) Radiology 43 330 33 Oct 1944

survived the intraperitoneal administration of lethal doses of bacteria toxin A nonspecific antitoxin was present in both peritoneal fluid and blood serum in 24 hours of irradiation and reached maximal concentration in 48 hours These observations suggested certain related problems for investigation

1 To determine if the response was peculiar to irradiation of peritoneum or abdominal viscera 12 rabbits were given 100 r each over the chest and 12 100 r over the extremities Forty eight hours later six animals from each group received a minimal lethal dose of diphtheria toxin (Eli Lilly & Co) and six a minimal lethal dose of hemolytic Escherichia coli toxin (prepared by the authors) Six rabbits served as controls three for each toxin

Of the irradiated animals none given diphtheria toxin died but three (two irradiated over the chest and one over the extremities) which had received hemolytic Escherichia coli toxin died All controls died within 48 hours This suggests that antitoxin is elaborated irrespective of the part of the body irradiated If the sole benefit from irradiation in the treatment of infections is production of antitoxins it would be unnecessary to deliver the rays into the infected tissue

2 To determine the minimal dose required to produce antitoxin four groups of eight rabbits received irradiation over the abdomen of 50 30 20 and 10 r respectively The intensity of the beam was 20 r per minute measured in air and dosage was determined by duration of exposure All animals plus six untreated controls were given toxin 48 hours after exposure

Two fatalities occurred among the rabbits given 50 r one among those given 30 r two among those given 20 r and seven among those given 10 r Therefore the minimal effective dose of 20 r would seem as efficacious as larger doses in production of antitoxin

3 To determine the effect of direct irradiation of whole blood and plasma defibrinated blood and plasma from stock rabbits were irradiated with 100 r incu

bated at body temperature for 48 hours and divided into lots of 14 cc to each of which was added 1 M L D of hemolytic Escherichia coli toxin After four hours incubation, each lot was injected into the peritoneal cavity of a rabbit For controls, 18 rabbits received serum and plasma similarly processed but not irradiated Six rabbits received just toxin

Of the rabbits given irradiated plasma (13) and blood serum (9) 3 in each group survived and 1 animal (plasma) died immediately without demonstrable cause Of the nine animals receiving unirradiated plasma toxin mixture, two survived, and of the nine receiving serum toxin four The six rabbits given toxin alone died These data suggest that plasma and serum injections afforded some protection the unirradiated as much as the treated Protection may have resulted from the antitoxin normally present in blood serum and plasma or from the minimizing of toxin shock

[This interesting report may explain the therapeutic effect of x rays in such infections as erysipelas —Ed]

DISEASES OF THE CHEST

(EXCEPTING THE HEART)

J BURNS AMBERSON M D

PART II
DISEASES OF THE CHEST

ANATOMIC STUDIES

Segments and Blood Vessels of Lungs It is now generally recognized that division of lungs into lobes is superficial and that there are smaller units known as bronchopulmonary segments or territories of ventilation A B Appleton[1] (Univ of London) describes the individual variations in pattern of the bronchial tree and pulmonary vessels as observed on dissection of 100 lungs and in a study of embryologic development

Bronchial Tree —The right upper lobe bronchus usually divides into three bronchi ventilating corresponding segments pectoral apical and posterior (Fig 2) There may be four openings (Fig 2) separated by main and secondary keels Differences arise in two ways The first axillary branch of either the pectoral or the posterior bronchus may open directly into the upper lobe bronchus (Fig 2 *B* and *C*) or two of the three bronchi may share a common opening into the upper lobe bronchus or if a secondary keel is overlooked appear to share a common opening (Fig 2 *B* and *C*)

The right middle lobe occasionally shows a vertical fissure which separates the axillary and medial segments There may be a *horizontal cleft* which divides the medial part into upper and lower segments This cleft may be mistaken for the true horizontal fissure if the latter is absent This should be considered when performing lobectomy

The pattern of the orifices opening into the left upper lobe bronchus differs from that of the right side Commonly it divides into ascending and lingular bronchi (Fig 3 *C*) Two orifices are thus recognizable opening

(1) L et 59 94 N 4 1944

into the upper lobe bronchus, separated by a horizontal keel In some lungs bronchoscopy of the upper lobe shows a slitlike aperture between two keels (Fig 3, *D*) Three orifices are thus visible the middle one opening into the pectoral bronchus A variant of this is a "trefoil" arrangement of orifices (Fig 3 *E*)

There is a cardiac segment in the lower lobe of each lung larger in the left This may extend farther forward than is usual i e to the interlobar, even to the costal, surface A cleft marking off this segment is sometimes seen on the mediastinal surface and in exceptional cases it has been found on the costal surface

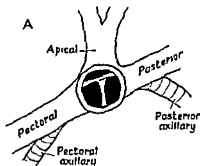
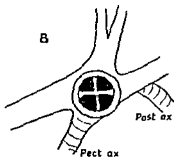
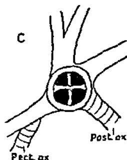


FIG ?—Var t s l branching of r ght upper lobe bronchus types with ho izo tal keel Types *B* a d *C* m y b nf sed and both l able to confu i n w th type *A* if pper keel s e looked.





Arteries and Veins—The arteries and veins of the lungs present very different relationships The arteries accompany minor bronchi closely the two together forming an arteriobronchial axis to the segment The larger veins are situated in the connective tissue planes between

the segments and collect blood from adjacent segments

The upper division of the right pulmonary artery provides arteries for the pectoral apical and posterior segments of the upper lobe One two or three ascending arteries also enter the lower part of this lobe from the lower division Different appearances in the branching of the upper division are due to (1) early division of the pectoral artery into two (2) early division of the apical

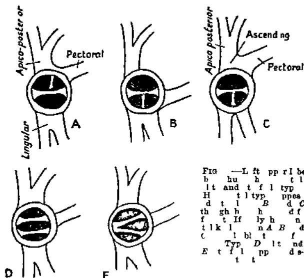


FIG —L ft pp r l be h hu h t l l t and t f l typ H t l typ ppea d t l *B* d *C* th gh h h d f f t If ly h n t l k l n *A* *B* d (l bl t f Typ *D* l t nd *E* t f l pp d s- t t

artery into two and (3) presence or absence of a recurrent branch to the posterior segment The lower division of the artery is the sole supply of the middle and lower lobes

The left pulmonary artery in arching over the upper lobe bronchus provides arteries for the apical and posterior bronchi The artery for the pectoral bronchus occasionally arises anteriorly before the arch more often it arises afterward and is then below the origin of the artery of the dorsal segment of the lower lobe In this situation care is needed if the pulmonary arterial sup-

ply to one lobe is to be left intact when the other is removed. The lingular artery usually arises after the main artery has arched over the bronchus, it then passes forward below the bronchus.

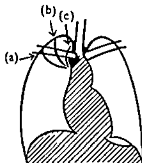
The larger collecting veins lie in the periphery of the various segments. They are therefore found between segments on interlobar surfaces or on the mediastinal aspect of the lungs. They are generally absent on costal and diaphragmatic surfaces. The veins drain adjacent segments and therefore form an anastomosing system throughout the lobes and where fissures are incomplete from one lobe to another. When the pulmonary arterial supply fails the venous anastomoses may contribute to vitality of these respiratory portions of the lungs which are not ordinarily served by bronchial arteries. The commonest situation for a vein communicating between lobes is the posteromedial part of the right oblique fissure. A large vein may carry blood from the dorsal segment of the lower lobe to the inferior pulmonary vein. This variation has been mistakenly described as "superior pulmonary vein" running down behind the root of the lung.

[This careful study is of great value for anatomic orientation not only in thoracic surgery but also in diagnostic procedures, especially when interpreting bronchograms. Since the fissures of the lungs are often incomplete or absent, the vascular supply in these anomalous circumstances should be well known.—Ed.]

Tomographic Appearance of Azygos Lobe. The azygos lobe, or accessory lobe of the azygos vein, results, according to Stibbe, from alteration in the relationship of the developing lung to the azygos vein. In early embryonic life the azygos vein runs over the right apex; as the lung grows the vein is pulled down by the heart, sliding over the medial aspect of the lung and finally arching over the right bronchus. If this sliding movement is arrested owing to some primary abnormality in position of the vein, the vein remains over the apex, producing an indentation which becomes deeper as the lung grows; this indentation is lined by a double fold of pleura carried down by the vein as it sinks toward the root of the lung and constitutes the azygos fissure. Based on anatomic

dissections Stibbe summarized the position of this fissure as follows (a) nearly horizontal cutting the lateral surface of the lung about 1–2 in below the apex (b) nearly vertical dividing the apex of the lung into approximately two equal parts (c) vertical cutting off a small tongue shaped lobe from the mediastinal surface (Fig 4)

J H Crawford reports on seven instances of azygos lobe observed at Preston Hall in a series of 6 000 consecutive films an incidence of 0 11 per cent Distribution of the azygos fissure was in position (a) one in position (b) four and in position (c) two The radiologic findings in one of two cases are given here





Fi 4 (l ft) —D ff p t s f yg fi
Fig 5 (ght)

Case 1 —Man 6 was adn tte l w th n ll basal pleural ffu s on on the right side The o d na v x a film of the chest (Fig 5) showed the characteristic th n shit curv d l ne in the r ght upper field approximately b se t g the apex (position b) th shadow of the azygos vein wa not cl arl visualized The median tomograph (Fig 6) tak n 11 m from the skin of the back revealed clearly the azygos vein as a globular pear shaped opacity The fissure was well delineated and the a ygos lobe was le s translucent than the rest of the lung It was s en that the azygos lobe was suppl ed from the eparte al bronchus The dorsal tomograph (Fig) taken at 8 cm from the back sl owed the

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FI 8 (t p) —Ab f l ft th b
F G 9 (bott m) —T g f tg gr m n F gu 8

masses alongside the notochord From each pair of primordia growth occurs in three principal directions mesially surrounding the notochord and producing the vertebral body dorsally flanking the neural tube and forming the vertebral arch ventrolaterally forming the costal processes from which the ribs originate The denser portion alone sprouts off the processes that become the vertebral arch and the rib (Fig 10) Any factor which

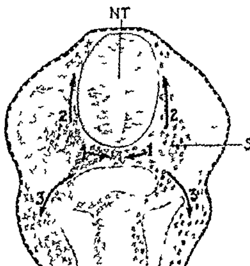


Fig 1 [illegible]

inhibits growth of the primordium of the rib may also interfere with the primordium of the vertebral body or arch

Aplasia of ribs and associated vertebral anomalies are most plausibly explained by Stockard's theory of malformation *At critical moments in the development of every organ or part which are characterized by rapid cell multiplication this proliferating region is dominant and may depress the growth of other parts* If this favorable moment of differentiation is not taken advantage

of the transient supremacy of the part is lost and it in turn submits to suppression by other parts The result is a reduced or imperfectly formed region which cannot compete with other parts now arrived at similar states of preferment Each organ or part therefore not only originates from a definite primordium but also arises at a definite moment that must be utilized then The factors most frequently responsible for defects are changes in moisture temperature and oxygen supply

[Another interesting and related study is that by Gershon Cohen and Delbridge Pseudarthrosis Synchondroses and Other Anomalies of the First Ribs *American Journal of Roentgenology and Radium Therapy* 49 64 January 1945 —Ed]

FUNCTION IN NORMAL AND ABNORMAL CIRCUMSTANCES

Recent Developments in Respiratory Physiology Related to Anesthesia are pointed out by Carl F Schmidt[4] (Univ of Pennsylvania) The oxygen saturation of arterial blood of normal men quietly breathing ambient air at sea level is of the order of 99 per cent instead of 93–96 and its tension of the order of 95–100 mm Hg instead of 80 or less The arterial oxygen tension agrees closely with that of alveolar air collected at the end of a quiet expiration but is lower than that in the end inspiratory samples that are widely used in this country

Dyspnea as produced intentionally in normal subjects in the laboratory or as encountered in the course of disease is due much more to the new or augmented reflex influences than to increased stimulation of the respiratory center by chemical products of metabolism Anesthetic drugs without exception make the respiratory center less reactive to chemical stimuli a tendency which may be counteracted by onset of excitatory nerve impulses (from the lungs and limbs in case of ether from the carotid and aortic bodies if anoxemia is present) but which otherwise may lead to early cessation of respiration (as with cyclopropane as usually given in a closed system with high oxygen tension)

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In the normal experimental animal severe anoxemia causes an immediate and marked increase in depth of respiration and on removal of anoxemia breathing is promptly depressed perhaps to the point of apnea with gradual return to normal In the denervated animal there is a latent period in which breathing is depressed followed by a progressive increase in rate and on removal of anoxemia respiratory stimulation comes on gradually and lasts for some time This is interpreted as indicating that in its direct effect on the cells of the respiratory center anoxia is both depressant and stimulant that the depressant effect may be overcome by chemoreceptor reflexes or if they are lacking by a slow building up of the stimulant process when the anoxia is remedied the depressant phenomena are removed more promptly than the stimulant

Direct studies of the oxygen consumption of the brain in situ have shown that cerebral metabolic activity runs parallel to cerebral functional activity and that convulsants may lead to cerebral anoxia (with all its consequences) because they increase the oxygen demand beyond the available supply In conditions in which cerebral anoxia is unavoidable its effects may be ameliorated by judicious use of narcotic drugs to lessen demand of the brain for oxygen The circumstances would have to be such that cerebral functions need not be retained and the underlying condition is not one of spontaneously increasing severity these requirements are met by severe carbon monoxide poisoning or by other agents that interfere with transport of oxygen by the blood, by severe hemorrhage or shock and by anesthesia involving anoxemia In such cases convulsant drugs seem to be contraindicated

A new method developed by Kety for measuring cerebral blood flow and metabolism has been used on a number of human subjects

[A better understanding of the physiologic mechanisms in anesthesia not only will permit better control of the immediate and direct effects but also will help to avoid sequelae such as postoperative pulmonary complications —F I]

Influence of Different Forms of Mechanical Artificial Respiration on Pulmonary and Systemic Blood Pressure was studied by Perry P Volpitto Robert A Woodbury and Benedict E Abreu[5] (Univ of Georgia) using seven different resuscitators An improved technic was developed for measuring the effective pulmonary and systemic pressure in animals with closed chest and without use of anesthetic

When respiratory arrest and slow weak cardiac contractions were produced by helium using the carbon dioxide absorption technic the animals recovered with any method of resuscitation Regardless of method immediate effects on pulmonary and systemic blood pressures of the hypoxic animals were similar Any blood flow which was produced by the resuscitators did not reach the coronary and cerebral arteries instead blood was pushed toward the extremities and cutaneous areas Intrapulmonic positive pressure of 10–12 mm Hg did not significantly hinder venous return This agrees with the clinical observation that increase in intrathoracic pressure in patients with congestive heart failure does not materially hinder venous return to the heart However intrapulmonic positive pressure above 10–12 mm if maintained for a prolonged period may hinder such venous return The experiments did not substantiate the theory that resuscitators employing positive negative pressures could empty or milk enough blood from the capillaries of the lungs to increase effectively the return of blood to the heart

When cardiac and respiratory arrest was produced with helium or by electrically induced ventricular fibrillation no respirator produced recovery Again regardless of the method used pressure changes were not significant These results however differed from effects of deep spontaneous breathing and dying gasps which repeatedly increased venous return to the right ventricle and pulmonary vessels and moved some blood from the pulmonary vessels into the left ventricle

(5) J A M A 1 6 1066 106 Dec 23 1944

Application of the Eve Rocking Method of Resuscitation on Shipboard is described by Samuel D Murray[6] (M C, U S N R) With this method the victim is changed alternately from a partial upright to a partial inverted position by vertical movement of a litter on a central fulcrum The weight of the stretcher, to which the subject is strapped face down is borne by supports leaving the operator free to produce the necessary movement i e a position of head down feet up to a 45 degree angle alternated with head up feet down to 45 degrees After a few minutes the arc is diminished to 30 degrees A face down position is recommended to facilitate drainage of water from the respiratory system and to forestall glossoptosis Eve warns that so efficient is this method care must be taken to restrict the motion to 10 double rocks a minute lest acapnia supervene

The method may be used on United States naval vessels with minor alterations to two types of litters available The Stokes litter may be used by welding eyes to accommodate a length of 1 in pipe to each side of the uppermost bar at the center of gravity arranged so that they may be turned down when the litters are stowed When the litter is in use the uprights are turned into position the length of pipe is inserted through the two eyes and the litter is suspended With extremities of the pipe supported on boxes or lifeboat gunwales or even held by stretcher bearers resuscitation may be undertaken at once by rocking the litter A rigid support such as a length of a pipe is desirable however lacking this cable, line or wire may be used The Army type litter may be adapted by having two eyes welded to the center of each shaft on the underside to accommodate the length of pipe The shafts should be reinforced at this point

Aside from the physiologic advantages this method of resuscitation requires no trained personnel is not tiresome and may be begun at the scene of the accident and continued during transportation two or more stretcher

(6) U S Nav M Bull. 44 161 165 Ja ry 1945

bearers being assigned to the supporting pipe and one delegated to rock the litter

[The article by Tingley (following article) should be consulted for information regarding the rate of artificial respiration in cases of asphyxia due to drowning etc —Ed]

Artificial Respiration Need for Greatly Increased Rate in Asphyxia P R Tingley[7] states that the usual rate of 15 times a minute is adequate for artificial respiration in cases without asphyxia such as under anesthesia and in electric shock but is inadequate in cases of asphyxia i e suffocation and cyanosis from drowning from lack of air (buried in bomb debris) or from smoke gases etc The depths of asphyxia may arbitrarily be divided into three degrees (1) up to loss of consciousness (2) up to cessation of respiration and (3) up to final heart failure Experiments in degree 1 asphyxia with a subject who held his breath for varying periods led to several conclusions The deeper the asphyxia the greater the respiratory requirement In any asphyxia necessitating artificial respiration the respiratory requirement must be greatly in excess of eight times the normal resting requirement The deeper degrees of asphyxia require a greater respiratory exchange to give appreciable relief The total volume of air exchanged in a given time largely determines the extent of relief from asphyxia the faster the rate of tidal respiration the greater the relief

Degree 3 asphyxia should respond to increased respiratory exchange in the same manner as degree 1 asphyxia provided the circulation is adequate to take up and distribute the extra oxygen made available As hopelessly inadequate circulation cannot be recognized on examination the safe method in all cases is to use as rapid a rate as possible In natural respiration for even mild asphyxia there is no time for pause inspiration and expiration being as quick and following each other as rapidly as possible In artificial respiration the same rate should be provided

In Schaefer s method the rate may be increased with

(7) Ls t 366 367 S pt 16 1944

out undue effort, to 30 times a minute and in desperate cases, with greater effort, to 60 times a minute without any loss of volume of respiration Silvester's method because of the nature of movements takes more time than Schaefer's and a rate of 45 times a minute seems to be the efficient maximum The same rule, as fast as possible without sacrifice in volume, applies to Eve's and other methods

[Consult the 1944 YEAR BOOK OF GENERAL MEDICINE for articles by Drinker (p 272) and Eve (p 274) on artificial respiration —Ed]

Application of Pulmonary Physiology to Therapeutic Procedures with Special Reference to Use of Oxygen Cecil K Drinker[8] (Harvard Univ) states that since carbon dioxide diffuses rapidly through a watery medium its concentration in the respiratory center and consequent stimulation of breathing depends on the condition of the center Ether alcohol chloroform, morphine and the barbiturates depress the respiratory center Far more important however than any drug for its dampening effect on the respiratory center is lack of oxygen This means that the essential automatic discharge of impulses by the center as a result of concentration of carbon dioxide is progressively hindered as anoxia progresses and thus anoxia produces anoxia

If oxygen lack is accompanied by gradual loss of efficiency in the central mechanism controlling breathing and thus by depreciation of oxygen intake its effect on the smallest blood vessels is even more significant According to Krogh anoxia is responsible for dilatation of the capillaries through a special form of chemical injury Although the pulmonary capillaries do not actively contract and dilate as do the systemic capillaries anoxia makes these vessels leak abnormally Of the factors leading to edema of the lungs increased permeability of the pulmonary capillaries is the most important and *of all the factors inducing it anoxia is the most frequent* The endothelium of the lung capillaries receives oxygen directly from the air *and not from the blood This makes*

(8) New England J Med 231 477 49 Oct 5

the lung capillaries dependent on the oxygen content of the alveoli in whose walls they lie Once the transuda tion from the capillaries has begun the lungs have no adequate means of getting rid of exudates Obviously exudates interfere profoundly with entrance of air into the alveoli and passage of oxygen into the capillaries So in the lungs as in the respiratory center anoxia produces anoxia

Since anoxia is progressive the time to begin oxygen therapy is before there is any certainty that it is needed Pure oxygen has five times the power of air oxygen to penetrate exudates and reach anoxic parts of the lungs and the blood going through them It should be given with minor interruptions so as not to irritate respiratory passages Oxygen tents often leak and the concentration is usually below 60 per cent Administration of oxygen by mask has been improved Morphine is valuable in re lieving dyspnea but it dampens the respiratory center and thus promotes anoxia This can be avoided by com bining it with use of oxygen Similarly after operations, especially in elderly patients with fairly rigid chests and pain on breathing that still further restricts respiratory movement oxygen therapy permits the economy of lung movement that the patient involuntarily provides and minimizes the danger of the much needed sedative

[Kritzler (*War Medicin* 6 69 3, December 1944) reports his study of 2 autopsies on members of high altitude bomber crews whose deaths had been attributed to anoxia He found wide pread severe capillary congestion particularly in the pulmonary renal intestinal and cerebral capillaries as well as other changes For other information on the phys ologic effect of anoxia on the lungs see also an art cle by Drinker in the 1943 YEAR BOOK OF GENERAL MEDICINE p 159 —Ed]

Oxygen Toxicity The effect of inhalation of high con centration of oxygen for 24 hours on normal men aged 19–31 at sea level and at a simulated altitude of 18 000 ft was studied by Julius H Comroe Jr Robert D Dripps Paul R Dumke and Margo Deming[9] (Univ of Pennsylvania) Substernal distress was produced in 82 per cent of 34 subjects breathing 100 per cent oxygen

(9) J A M A 1 8 710 717 J ly 7 194

continuously for 24 hours at sea level The symptoms were quite similar to those of mild 'chokes and were noted on an average at 14 hours after the start of oxygen administration Forty three per cent developed nasal congestion or coryza, 32 per cent sore throat and 54 per cent occasional or repeated cough Twenty three per cent had conjunctival irritation The distribution of the substernal pain and its aggravation by inhalation of dry cool ambient air cigaret smoking and deep breathing suggested the existence of tracheobronchitis Sixty three per cent of 80 subjects breathing 50 75 and 100 per cent oxygen showed a decreased vital capacity Twenty five per cent of those breathing 100 per cent oxygen continuously developed ear discomfort whereas only 5 per cent of those breathing 100 per cent oxygen intermittently developed this symptom The inhalation of high concentrations of oxygen for 24 hours had no appreciable effect on the formed elements of blood pulse rate blood pressure or respiratory rate

Control subjects breathing room air through the same apparatus did not experience any symptoms Seventy five per cent oxygen produced symptoms in only 55 per cent of the subjects 50 per cent oxygen produced no symptoms during the 24 hour period Since oxygen tents or catheters rarely produce alveolar oxygen concentrations higher than 50 per cent these forms of administering oxygen are completely safe Breathing of 100 per cent oxygen at high altitudes (low total atmospheric pressures) does not produce symptoms indicating that the symptoms are caused by high oxygen tensions and not by elimination of nitrogen Use of 100 per cent oxygen for short periods is probably safe in all patients but when oxygen must be given in excess of 12 hours the following rules should be followed (1) the oxygen concentration should be reduced to 60 per cent unless this is insufficient to saturate the arterial blood and (2) if 100 per cent oxygen must be given a careful check should be made for the symptoms most likely to occur as a result of the high tension of oxygen

[Oxygen toxicity is not observed during ordinary clinical administration but may become a problem in high altitude flying. This and the following study are therefore of value in understanding the effects.—Ed.]

Effect of High Oxygen Tension on Respiratory System Julius Kaunitz[1] reports on experiments in mice exposed to 100 per cent oxygen for three days. All animals were apathetic at the end of the second day, showing no interest in food or drink. On the third day they became dyspneic and cyanotic and died, some in convulsions. The lungs were collapsed and dark red, had the consistency of liver and sank to the bottom of the formalin solution. The heart, liver and kidneys were dark red and swollen. Histologic examination disclosed interstitial edema of the trachea, bronchi and lungs, denudation of the epithelium of the trachea, and constriction and occlusion of the bronchi associated with atelectasis.

The pathologic changes in the respiratory tract are primarily due to the prolonged irritative effect of oxygen comparable with that of some war gases. Initially oxygen reaches the alveoli with ease. Later the bronchi show contraction and become filled with mucus and desquamated epithelium, resulting in obstruction of the air passages. The intra-alveolar gases are absorbed and as no more air enters, the pulmonary segment dependent on the obstructed bronchus collapses. The pulmonary collapse, edema and capillary stasis all affect the vital capacity until oxygenation of the blood is inadequate for life. Paradoxically this anoxia is caused by high oxygen tension. Despite the harm caused by the pure oxygen the animals are dependent on it to such a degree that transference to a normal atmosphere at any time during their last six hours results in instant death. The anoxemia also causes damage to the myocardium and other vital organs.

Comparison of Altitude and Exercise with Respect to Decompression Sickness S. F. Cook, O. L. Williams, W. R. Lyons and J. H. Lawrence (Univ. of California) performed pressure chamber tests with four groups of

(1) J. Mt. S. H. p. 1. 411-415 My-Jn 1945
(2) W. M. d. 6 18 187 S. pt. b. 1944

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scent of 25 cases in which chokes caused descent 13 were moderate and 12 severe In general men with moderate and severe cases showed a greater intensity of cough than did men with incipient and mild cases Pain was important in judging severity of the condition There appeared to be a significant though low degree of association between chokes and joint pain onset of the former tending to occur after onset of the latter

Increasing the altitude produced a great difference in the intensity of chest pain whereas increasing the exercise did not alter severity of chest symptoms If the use of oxygen and rate of ascent are kept constant the severity of tests in the decompression chamber is influenced by altitude and by the amount of exercise performed at altitude A test at a higher altitude with more exercise is more severe than one at a lower altitude with less exercise As severity of the chamber test increases (1) the percentage incidence of chokes among individuals who have joint pains increases (2) the percentage incidence of descents caused by chokes among subjects who have chokes increases and (3) the curves reflect a law of diminishing returns i e they tend to level off Chokes occurred with approximately the same frequency in the morning as they did in the afternoon The mean age of subjects who developed chokes was identical with that of subjects having no chokes 19 4 years

Bronchospirometry Max Pinner George C Leiner and William A Zavod[4] (New York City) present a summary of the results of bronchospirometric studies carried out at Montefiore Hospital for the last 5½ years By bronchospirometry functions and volumes of each lung are determined separately and simultaneously Substitution of a soft rubber tube for the metal bronchoscope has made the method less uncomfortable for the patient and the results more reliable Bronchospirometry is indicated whenever an irreversible operation on one lung is contemplated to determine the functional capacity of the contralateral lung It also permits study of

(4) I t M d 704 718 M y 1945

healthy men 18–20 Two groups were maintained at 30,000 ft for 90 minutes The men performed the standard exercise (ten 9 in step ups in 30 seconds) every 5 minutes in one group every 2½ minutes in the other The third and fourth groups were taken to 38,000 ft and were similarly exercised The bends-inducing effects of the four sets of conditions were judged on the basis of per cent incidence of symptoms per cent incapacitation time of onset of symptoms time of descent maximum intensity of symptoms and rapidity of their development All criteria revealed statistically important differences between the two altitudes with constant exercise At 30 000 ft the effect of doubling the frequency of the exercise was relatively slight and not always statistically significant At 38 000 ft the effect of increase in exercise was significant with most criteria but was much less marked than the effect of changing altitude

The authors conclude that increase in altitude from 30 000 to 38 000 ft increases the incidence and severity of decompression sickness considerably more than doubling the muscular work by increased exercise

Chokes Respiratory Manifestation of Aero-embolism in High Altitude Flying Ezra V Bridge Franklin M Henry Owen L Williams and John H Lawrence[3] (Univ of California) made studies on 132 cases of chokes occurring in 329 young men making 719 flights ' in a decompression chamber Chokes [supposed by some to be due to gas emboli in venous blood arrested in pulmonary capillaries —Ed] are recognized by three major symptoms substernal nonradiating pain cough and dyspnea The pain is usually relieved during descent while the cough usually continues and may become intensified during recompression Dyspnea appears in the more severe cases Of the cases studied 40 were incipient, 43 mild 33 moderate and 16 severe 78 per cent of the men affected had pain 50 8 had cough or desire to cough and 12 1 per cent had dyspnea In no case did incipient or mild chokes cause premature de

(3) An Int M d 2 398 407 M h 1945

thorax treatment frequently show extensive functional impairment Change in the patient s posture from the recumbent to the left or right side does not affect the percentage distribution of the vital capacity between the left and right lungs Attempts at immobilizing a hemi thorax by sandbags weighing up to 20 lb and by strap ping with adhesive tape do not reduce the ventilation or respiratory work of the underlying lung

[The importance of determining the function of each lung separately when artificial pneumoth rax and maj r surgery are being contemplated s lf evident since it is des rable not only to alleviate or to c i e the pulmonary disea e but also to preserve maximal funct on. The permanent funct onal impairment produced by pneumothorax parti ularly when complicated with chronic pleur y mu t be weighe l in the deci i n for o aga nst this form of treatment It may be nferred from the e studies that lateral recumbent postures have l ttle or no appreciable effect in resting the diseased lung Nevertheles such postures may be of value in promoting proper bronchial drainage an l in avo ding trans bronchial spread of infection to the healthy lung —Ed]

Ventilatory Function Experience with a Simple ***Practical Procedure for Its Evaluation in Patients with*** **Pulmonary Tuberculosis** is presented by Frederick C Warring Jr[5] (Laurel Heights Sanatorium Shelton Conn) Dyspnea (ventilatory insufficiency) results from a decrease in the maximal breathing capacity or an in crease in the breathing requirement or a combination of the two The maximal breathing capacity was deter mined by having the patient in a sitting position apply ing a nose clip and telling him to breathe as hard and as fast as possible for 30 seconds through a high velocity one way valve into a 100 L Douglas bag The total ex pired air was measured by passing it through a meter and the result multiplied by two gave the maximal breathing capacity in liters per minute

To evaluate the adequate breathing requirement of each patient a simple test was developed consisting of determination of walking ventilation This was meas ured by using the same apparatus as for the maximal breathing capacity The nose clip was applied and the patient walked over a measured level course accompa

(5) Am R T b 1 4 454 M 1945

various physiopathologic problems of respiration especially those concerned with the compensatory mechanisms which are elicited in one lung by disease or operative procedures (collapse measures lobectomy) Contraindications to bronchospirometry are tuberculous ulcerations of the larynx and to a lesser extent of the trachea or bronchi hyperpyrexia recent hemoptysis or serious illness

The authors attempted bronchospirometry 380 times and obtained 270 satisfactory records In no patient has there been a serious accident All patients in whom bronchospirometric studies were done were also examined by spirometry Bronchospirometry often revealed abnormal functions of one lung when the spirometric findings were normal or nearly normal Bronchospirometry also occasionally revealed certain findings which were not *suggested by roentgen and clinical observations* The studies also showed that pleural involvement often causes severe functional damage of the lung while parenchymal lesions may have relatively little effect on pulmonary function Studies of 18 patients before and several months after induction of unilateral pneumothorax indicated that collapse reduces the oxygen intake of the collapsed lung decreases the minute volume tidal air vital capacity reserve air and complementary air and increases the ventilation equivalent Compensation is achieved by an increase of the oxygen intake in the contralateral lung which is done only partially by increased ventilation oxygen intake is further increased by better utilization of the ventilated oxygen i e a decrease of the ventilation equivalent The contralateral effect of unilateral pneumothorax is manifested by a decrease in vital capacity reserve and complementary air of the contralateral lung

Thoracoplasty causes similar functional changes but on the average these changes are less severe than those during collapse therapy by pneumothorax and in some cases than those in lungs *following abandonment of* pneumothorax Lungs re expanded following pneumo

imminence of dyspnea in patients with tuberculosis receiving other types of therapy than thoracoplasty and in patients with conditions other than tuberculosis

Warring concludes that there is a need for simplified procedures to evaluate pulmonary function and objectively to determine or predict pulmonary insufficiency which can be used in the smaller sanatoriums and hospitals or in the physician s office unequipped for more elaborate tests Determination of the maximal breathing capacity (repeated at necessary intervals) and the walking ventilation together with fluoroscopic examination will give a picture of the status of pulmonary function adequate for practical purposes in most patients Special training on the part of the operator or patient is not necessary the apparatus is inexpensive and relatively simple to operate

[This modification of a standard exercise test has the virtue of comfort and convenience In many cases if facilities are available it is desirable to carry out much more elaborate functional studies —Ed]

Influence of Ingestion of Food on Ventilatory Capacity of Lung Jorge Alberto Pilheu[6] carried out spirometric studies on 51 subjects before and after regular meals investigating the inspiratory apneic pause vital capacity and maximal respiratory volume Normal controls cardiac and tuberculous patients and a few psychopathic persons were included in the study All complained of a sensation of fulness after meals accompanied by general depression muscular weakness and mild dyspnea this sensation being more marked in the cardiac and tuberculous patients

Variations obtained in the three indexes of respiratory function after meals were too small to have statistical significance Of the three factors only the inspiratory apneic pause was constantly diminished after meals This index however is not of great significance in determination of the ventilatory capacity of the lungs since it is also influenced by the state of circulation by the psychic state etc The vital capacity was diminished

(6) M d Bu A s 5 53 64 Ap 1 1945

nied by the operator covering 180 ft in one minute For the first minute the patient walked without breathing into the tube After this 'warming up' period he walked for three more minutes holding the valve and breathing normally into the bag held by the operator After completion of the test the degree of dyspnea (slight moderate or severe) was recorded The expired air was measured and the result divided by three gave the walking ventilation in liters per minute The amount varied from 8 to 30 L per minute A definite correlation was found between the walking ventilation maximal breathing capacity ratio and the degree of dyspnea present when walking In most patients the walking ventilation remained constant for as long as 22 months It was therefore utilized as a base line for the breathing requirements of the individual patient It was postulated that collapse therapy should not reduce the maximal breathing capacity below twice the value of the walking ventilation i e the ratio should not exceed 0 50 if the patient was to avoid severe dyspnea when ambulatory

The maximal breathing capacity and walking ventilation were determined in 26 patients before and after thoracoplasty At the same time motion of the ribs and diaphragm and mediastinal shift were observed through the fluoroscope The maximal breathing capacity was reduced following operation in 25 of the patients in many of them materially and in a few as much as 30-40 L In only five patients did the walking ventilation change 5 L or more following thoracoplasty The large majority of these thoracoplasties included eight ribs or more with long sections of the ribs being removed *The* long term postoperative application of tight pressure binders may have been a contributing factor The maximal breathing capacity measured 13 days after each stage of the operation gave a true picture of ventilatory function at those times and was a reliable indication of the ability *of the patient to undergo further operation*

The method of studying ventilatory function as described was found useful *in evaluating the* ... or

medial portion of the right lower chest or tympany if the herniated bowel is distended with gas The heart may be displaced to the left

Roentgenography shows density over the lower portion of the right lung field adjoining the heart border



Fig 11—P ter l diaphragm t h n b um n m tud sh w d lt l R u d d f m ttled d n ty n ght l wer lu g fi ld h rt h d w d pl d sl ghtly t l ft L p f b w l th vity gta n g s, p du ng f n ed d n p r riebr l p rt n f ght m ddl nd l w lung fi ld

and extending laterally sometimes across the chest to the axilla The density may be uniform if the hernia contains only omentum or bowel filled with fluid obscuring the outlines of the right diaphragm lower ribs and heart border The density is rounded with sharply defined borders If the colon contains gas colonic haustra

after meals in some and increased in others whereas the maximal respiratory volume showed more increases than diminutions Although the sensation of postprandial distress is not *as marked as the dyspnea of the cardiac* or asthmatic patients it is a similar sensation Pilheu believes that it may be due to the greater effort of the diaphragm which has to overcome a major resistance—*in this case that of a full stomach,* to maintain a normal vital capacity and maximal respiratory volume

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RESULTS OF PHYSICAL ABNORMALITY OR INJURY

Parasternal Diaphragmatic Hernia Despite the rarity *of this condition* judged by the small number of cases reported, Max Ritvo and O S Peterson Jr[7] (Boston) believe that it has often been misinterpreted as thoracic neoplasm and that there are actually more cases in existence than the number recorded The hernia often presents a characteristic roentgen appearance and can be diagnosed by roentgenography and roentgenoscopy They *have diagnosed* six cases *most of them from roentgen* findings

The lesion has been found at all ages from a few days after birth to old age There is no particular sex incidence The hernia usually includes omentum and transverse colon less frequently it includes the ascending colon cecum appendix and terminal ileum Many patients have no complaints referable to the lesion others have symptoms simulating ulcer or gallbladder disease and still others have bizarre or atypical syndromes Severe constipation is common Strangulation and obstruction are reported in 10–15 per cent of cases Chest complaints include cough dyspnea and precordial pain Often symptoms are referred to chest alone and mechanical interference with breathing and lung expansion leads to an erroneous diagnosis of lung tumor Physical examination usually discloses dulness over the antero

(7) Am J Roe tg n l 5 399 405 O t be 1944

ment of the adjacent portion of the colon toward the midline of the upper abdomen There may be separation of afferent and efferent loops Frequently the colon is narrowed at the point of passage through the opening in the diaphragm The stomach and jejunum are not involved and are in normal position

Treatment is conservative and expectant The condi



F o 13 —S m 8 4/3 y] t b m m i dy p e o t p j t n H t d l p f b w l fill l p rtly with b m d p rtly w th pwa d d m d d d pl m t f um and asc ding col n

tion may exist for years without progressing or causing symptoms Surgery is indicated in case of incarceration or strangulation unless relief is promptly obtained by enemas and other conservative procedures

Effects of Cold Air on Air Passages and Lungs were studied in dogs by Alan R Moritz and James R Weisiger[8] (Harvard Univ) The air was brought into the

(8) A h Int Med 75 2 3240 Ap il, 1945

tion may be seen which is pathognomonic for the condition In lateral projection, the mass occupies the anterior and middle portions of the right lower lung field and presents round smooth posterior margins, while merging anteriorly with the shadow of the chest wall With



FIG 1 —Same p e eding R und d de s ty t right ba e l w ll ante ly haracte t c n p ra te nal d aph gn t c h a g ta n ing loop of bowel n ant ri r a d super o parts of m s in r ght low r lung fi ld

this type of shadow parasternal hernia should be considered in the diagnosis unless eliminated Barium meal and opaque enema studies are important If only omentum is present there may be upward and mediad displacement of the right colon hepatic flexure and transverse colon With herniation of the colon a large loop of transverse colon lies above the diaphragm with displace

would be warmed to a point well above freezing before it reached the bronchi

Effects of Inhaled Heat on Air Passages and Lungs were investigated experimentally by Alan R Moritz Frederick C Henriques Jr and Regina McLean[9] (Harvard Univ) To study thermal injuries of the lungs independently of any complications that might be caused



FIG 14 —P imary thermal p m t low l b f d g's l ng 24 h u fte h l t n f st m Alth ugh th w e t h t s, p m ry nd se d ry b n h h w d rem k bly l ttl ch g E d f p lm n ry j ry nfi ed l g ly to ntral p rt f l b st d f hyper mia, ed m nd p rt l tel cta is

by concomitant burning of the skin the hot air was conveyed directly to the trachea by means of an insulated transoral cannula Three types of inhalation experiments were performed on dogs using (1) ordinary hot air at different external temperatures (2) flame and combustion products from a blast burner and (3) a mixture of live steam and air

Results revealed that only when the original temperature of the air was high enough to produce almost in

(9) Am J P th 21 311 331 M h, 1945

mouth and throat through a vacuum jacketed cannula and the animals were not otherwise exposed to cold The animals breathed extremely cold air for periods of 20-133 minutes The rate at which the air was warmed in the body was measured by thermocouples The air was delivered to the larynx at temperatures ranging between —50 and —28 C and in no instance was a temperature recording lower than 18 C observed at the bifurcation of the trachea Inhalation of cold air in circumstances such that intralaryngeal inspiratory nadirs of —30 C or lower were reached resulted in development of a localized sublaryngeal tracheitis In some animals the disturbance was limited to unusual activity of the mucous glands and in others there was focal destruction of the superficial epithelium In no instance did primary injury to the lower portion of the trachea, bronchi or lungs occur The aspiration of mucus or mucus and mucosal detritus from the upper portion of the trachea may result in development of small and evanescent foci of pulmonary emphysema and atelectasis

The explanation of the rapid warming of inhaled cold air and the occurrence of relatively mild and localized injury following inhalation of cold air lies in the facts that dry air has an extremely low heat capacity and that the number of calories required to produce a great rise in the temperature of dry air can be provided by the heat derived from the cooling of a small amount of tissue by a few degrees Although the intermittent exposure to cold air that occurs during normal respiration does not cause significant injury to pharynx or larynx a continuous exposure of these structures to cold may result in development of a rapid obstructive edema

The authors conclude from their experiments that significant injury to the air passages of man is improbable from the breathing of air at any degree of coldness likely to be encountered in nonexperimental conditions as long as it is inhaled through the nose or between partially closed lips and that even if extremely cold air were inhaled rapidly through a widely open mouth it

cosa dilatation of large and small bronchi hemorrhagic edema of the peribronchial connective tissue and generalized hyperemia and hemorrhagic edema of the peripheral and the central pulmonary parenchyma

[This contribution aids materially in understanding of the effects of inhaling flames or xce i ely h ated air or gases —Ed]

Pathogenesis of Pulmonary Atelectasis Paul F Vaccarezza[1] uses the term atelectasis in its etymological sense insufficiency of expansion of a part or all of the lung i e a state of alveolar relaxation The term implies an acquired process a similar congenital condition should be termed fetal state of the lung for alveolar development depends on the morphogenic function of the respiratory movements Atelectasis includes two modalities pulmonary collapse and apneumatosis The pulmonary or alveolar collapse can be subdivided into (1) physiologic retraction of the parenchyma resulting from elasticity of the organ and occurring in presence of pleural fluid phrenic paralysis thoracoplasty compression by a tumor etc or (2) pathologic retraction resulting from retractile fibrous processes frequently tuberculous (spontaneous clerosis or consequent to collapse therapy) Apneumatosis signifies a lung deprived of air and is generally but not invariably the result of bronchial obstruction Apneumatosis occurs in two forms simple or ischemic apneumatosis with a pale or gray lung the result of air resorption and alveolar relaxation and congestive or hyperemic apneumatosis with a red or red violaceous lung the result of air resorption alveolar relaxation and stagnation of blood with serous or serosanguineous transudation From the viewpoint of pathogenesis four types of atelectasis may be distinguished atelectasis by compression of the lung atelectasis by fibrous retraction of the parenchyma gas absorption following bronchial obstruction and atelectasis by alveolar adhesion (apneumatosis consequent to resorption of an exudate without ultimate penetration of the air into the alveoli—residual state after infiltration or after resorption of pneumonic process)

(1 S m mAd 5 (pp) 347 356 1945

stantaneous burning of the skin and upper respiratory mucosa was there sufficient residual heat in the air reaching the lungs to cause pulmonary injury No type of thermal pulmonary exposure was encountered which was immediately incompatible with life A thermal exposure *sufficient to injure the lungs was more than enough to* cause a rapidly fatal obstructive edema of the glottis Only when the larynx was protected against heat did animals survive long enough to develop the characteristic lesions of thermal pneumonitis At any given temperature moist air has more heat to give up than does an equal volume of dry air and is accordingly more likely



FIG 1 —Ob t u t e ed ma of gl tti due to inhal t on f h t a pharynx a d gl ttis of dog four hou aft r i h lation of a at 500 C F r t imp rt of a r wa b ve n t below glott

to cause thermal injury of the respiratory tract Inhalation of dry or moist hot air may destroy the upper tracheal mucosa without causing primary thermal injury of the lungs In the dog a severe thermal tracheitis predisposes to the development of bronchopneumonia The most vulnerable portion of the lung to thermal injury is the central parenchyma where the respiratory bronchioles and alveoli have the shortest and most direct connection with the primary bronchi In instances of mild thermal injury of the lungs the centrally located alveoli were the seat of hemorrhagic edema even though there had been *insufficient heat to cause recognizable injury* of the bronchial mucosa or the more peripherally located air sacs In instances of severe thermal injury of the lungs there were extensive destruction of bronchial mu

patient with vital capacity of 1 000 cc and arterial oxygen saturation of 60 per cent was orthopneic but only extremely so when exerted The patient in Case 2 with vital capacity of 1 800 cc and arterial oxygen saturation of 87 per cent was not much more restricted in activity than the patient in Case 3 who had vital capacity of 4 200 cc and oxygen saturation of 89 per cent Kymographic vital capacity recording demonstrated that the usual method of measuring vital capacity is misleading owing to neglect of the time factor A kymographic tracing in Case 3 revealed that whereas the patient had a vital capacity of 4 200 cc it took him 20 seconds to exhale the same amount of air a normal subject exhaled in 1½ second Although his vital capacity was normal only a small fraction of this was available in carrying out any respiratory function This marked limitation of exercise tolerance despite quantitatively normal capacity i explained on the basis of mechanical inability to ventilate the lungs

In the severest case (Case 1) history revealed repeated episodes of pulmonary infection and although adventitious sounds were *not* heard a bronchospastic factor was suggested by the paroxysmal nature of dyspnea its precipitation by emotion occasional presence of squeals and groans and relief of dyspnea for several months after pneumococcic pneumonia Presence of a bronchospastic factor was confirmed when administration of a few minims of a 1 100 solution of adrenalin by inhaled nebula resulted in a rise of vital capacity from 1 300 to 2 700 cc in seven minutes Adrenalin in oil in 1 cc doses injected every eight hours maintained vital capacity at 2 300 cc Adrenalin in nebula is one of the few valuable and readily applicable therapeutic measures in emphysema

Analyses of alveolar air and of arterial blood disclosed that in emphysematous patients the abnormal mechanical difficulties of respiration result even at rest in subnormal pulmonary ventilation and in varying degrees of adaptatio the resulting physiologic changes The poly

The blocking of a bronchus causes stoppage of ventilation and gradual absorption of the air trapped in the corresponding pulmonary segment The absorption of air proceeds according to rules governing diffusion of gases in normal respiration If following bronchial obstruction and initiation of gas absorption retraction of the lung (the usual sequence in such cases) is prevented by an obstacle of some kind the negative intra alveolar pressure which increases in proportion to the rate of absorbed air causes transudation of tissue fluids into the lumen of the acini transudation ex vacuo This transudate may be serous serosanguineous serocellular or fibrinous Its organization may lead to cornification and fibrosis of the parenchyma It has been demonstrated that atelectasis is incapable of causing sclerosis of the lung parenchyma unless infection of the involved area exists

The simple roentgen examination is generally insufficient to establish the diagnosis of atelectasis which is made on this basis too frequently and too readily There is no pathognomonic image of atelectasis When a homogeneous opacity with sign of retraction is found it is difficult to distinguish atelectasis from coexisting anatomic state such as alveolar exudation pulmonary suppuration or sclerosis The finding of such an opacity authorizes only a diagnosis of a syndrome of pulmonary retraction whatever its cause

[This article is of value in helping explain some of the mechanisms involved in atelectasis The condition is diagnosed in clinical medicine much more often than circumstances warrant The diagnosis is often serves merely to obscure an understanding of the real features involved Mere relaxation of alveoli does not in itself predispose to pneumonia but the accumulation of edema fluid does The latter frequently occurs without any evidence of alveolar relaxation or collapse So called infected atelectasis is usually a misnomer The infection is more often due to proliferation of inhaled micro-organisms in edema fluid a good culture medium —Ed]

Abnormal Physiology of Chronic Pulmonary Emphysema Three contrasting illustrative cases are reported by Alfred I Goggio (Harvard Univ) In Case 1 the

( ) New England J Med 31 67 677 Nov 16 1944

smaller bronchioles were an important factor in certain of them notably aspiration of amniotic fluid, acute infectious bronchiolitis and aspiration of zinc stearate bronchiolitic obstruction was the primary and most significant lesion In these cases the original obstruction is most probably the expansile check valve type described by Jackson and Jackson resulting from mucosal irritation and inflammation which produce edema and exudation When there is aspiration of foreign material the obstruction produced by it is an added factor Peribronchiolitic and interstitial changes are a secondary but important more or less constant accompaniment

Clinically there are certain similarities to asthma but in contrast with the usual relatively short duration and self limited course of the average attack of asthma even the acute forms of obstructive emphysema in infants tend to persist for a week or so and many of them for much longer The common features are an increased respiratory rate and markedly decreased respiratory excursions associated with utilization of the accessory muscles of respiration which results in an indrawing at the suprasternal notch and at the lower margin of the thorax This is not as marked as in severe laryngeal or tracheal block in which the obstruction is chiefly inspiratory in type In contrast with laryngeal obstruction there is usually no hoarseness or stridor in contrast with asthma there is no audible wheeze Cyanosis depends on degree of obstruction The percussion note is hyperresonant except over localized areas of consolidation and the respiratory murmur is characterized by prolongation and roughening of the expiratory phase On the roentgenogram the diaphragm is low and flattened the ribs are farther apart than usual and the lung fields less dense Of more significance is the fluoroscopic evidence of the markedly restricted excursions of the low and flattened diaphragm There may be a slight increase in the horizontal diameters of the chest during expiration suggesting that the emphysematous lungs are simply being forced into a different position rather than

cythemia found in Cases 1 and 3 was an adaptation to subnormal alveolar oxygen tensions Such patients live to some extent at high altitudes at sea level The symptoms found in emphysema which simulate mountain sickness should be attributed to anoxia They are relieved by oxygen and should not be ascribed to constipation Oxygen therapy is of value in preventing and breaking the vicious cycle of chronic anoxia embarrassment of physiologic functions and respiratory fatigue, with resultant increase in general well being and in exercise tolerance Discontinuous oxygen therapy over a long period is not so costly and can be used at home

[In these cases in which bronchospasm is a factor there is often an accumulation of sticky mucus in the trachea and bronchi and in addition to using a bronchodilator it may help to liquef the secretions by using steam inhalation Patients sometimes become well adapted to arterial oxygen unsaturation They may be better off without oxygen therapy except during some acute need since the restoration of full physiologic saturation may lessen their tolerance for low saturations when the therapy is discontinued —Ed]

Generalized Obstructive Emphysema in Infants Waldo E Nelson and Lawrence W Smith[3] (Temple Univ) present several cases to illustrate the variety of conditions in infancy in which diffuse bilateral obstructive emphysema has been observed This type of respiratory disturbance is not uncommon While in most of the infants observed the condition had an acute self limited course unaffected by sulfonamides and strongly suggestive of being the infantile counterpart of influenzal (virus) *pneumonitis or of so called primary atypical or* viral pneumonia there has been a variety of pathologic conditions which have been responsible for dyspnea in association with obstructive emphysema These included aspiration of amniotic contents during birth cystic fibrosis of the pancreas atypical bronchopneumonia, laryngotracheobronchitis miliary tuberculosis aspiration of zinc stearate powder and chronic passive congestion secondary to congenital heart lesion

In all of the conditions obstructive processes in the

(3) J Pediat 6 36 J 194

ties probably owing to the head down position in which the seaman was found suggests that carrying such casualties head down would lessen the distribution of air to the brain

Pulmonary Concussion (Blast) in Nonthoracic Battle Wounds is reported by Oswald Savage[5] (R A M C) Autopsies on 87 battle casualties showed some degree of blast lung in over a third assessed as severe (9 cases) moderate (10 cases) or slight (11 cases) on the basis of presence of consolidation area of lung involved and number of hemorrhages In 23 cases exposure to blast was certain and in 7 the method of wounding was unknown Most of the injuries were penetrating head wounds Most patients were unconscious while under observation *and none had external evidence of thoracic damage* None had hemoptysis Physical signs in the chest were minimal and confined to adventitious sounds scattered over the lungs more pronounced at the bases which is not unusual in a patient in coma Radiography showed evidence of intrapulmonary hemorrhage in the shape of a diffuse fluffy mottling The time between wounding and death varied from 1 hour to 85 days

The lungs were large in most the surfaces showed no change but on sectioning a striking spatter of hemorrhages was seen In some these coalesced to form areas of consolidation always in the lower lobes and frequently only in the posterior costophrenic fringes Circular areas of hemorrhage about 1 cm in diameter were scattered throughout the lung The lower lobes were mainly affected but on the average the distribution throughout a lobe was uniform from periphery to hilus In seven cases there were pinpoint hemorrhages in the parietal pleura Hemorrhages beneath the visceral pleura were present in 10 cases Occurring mostly around the roots of the lungs they bore no relation to the amount of bleeding in the lung parenchyma no lines of hemorrhage corresponding to the ribs were seen in this series In every case the trachea was free from

(5) L t 1 4 4 4 9 Apr 7 194

being emptied of any significant quantities of trapped air

While the pathologic lesions which are responsible for obstructive emphysema also occur in older children and adults the clinical pattern and respiratory embarrassment are more pronounced in infants probably due to the peculiarities of structure of infantile bronchiolar and interstitial tissue

[Extreme prolongation or recurrence of obstructive emphysema in infants may predispose to deformity of the thoracic wall Such cases therefore should not be taken lightly —Ed.]

Air Embolism in Diver Frank J Gouze[4] reports a case

Seaman 19 made a training dive to 40 ft After having ascended about 15 ft he began to pull on the life line this struggling stopped shortly and he gave no answer to signal. Another diver found him lying motionless in the mud his leg caught in the line 4 ft *from the bottom his mask around* the neck. Brought to the surface he was given resuscitation measures to no avail Autopsy disclosed emphysema of the lungs air emboli in the heart and blood vessels of the entire body and small recent infarcts in the lungs spleen kidneys and intestines.

Air embolism occurring as a diving accident is the result of the diver holding his breath during ascent As the pressure outside the chest decreases in ascending the intrapulmonic pressure is increased owing to expansion of the entrapped air This increased pressure produces a marked drop in pulmonary circulation by compression of the pulmonary vessels a consequent drop in blood pressure and ultimately lung rupture Pulmonary circulation is re established when the diver surfaces and exhales thereby relieving the excess pressure At this moment air enters the ruptured pulmonary vessels resulting in aero embolism In the present case restoration of pulmonary circulation and consequent release of air into the blood occurred when the diver loosing his hold on the line fell to the bottom Since much shallow water diving is being done by men with brief training medical officers should be on the alert for similar accidents The finding of few air bubbles in the vessels of the brain but many in the vessels of the lower extremi

(4) U S Na M. Bull 43 3 -4? Sept mbe 1944

damaged lungs Artificial respiration is contraindicated because of the danger of increasing pulmonary hemorrhage and the possibility of forcing the air into pulmonary veins nor should plasma be used for it may increase pulmonary hemorrhage and edema

Accidental Hanging with Recovery Mildred Kemper and Stanley Gibson[7] (Children's Memorial Hosp Chicago) report two cases in children Both had strikingly similar symptoms and signs varying only in severity and duration The cases reported in the literature likewise show a remarkably consistent clinical course The symptomatology usually includes unconsciousness and cessation of respiration for a time followed by violent convulsions and irrationality tachycardia rapid respirations dysphagia aphonia incontinence of urine and feces dilated pupils temperature elevation for several days and complete amnesia of the event and of 3–10 days before the event Recovery is almost always complete without residual damage in 10–14 days Treatment is largely supportive including immediate administration of oxygen by tent or nasal catheter hypertonic glucose intravenously and sedation with phenobarbital Phenobarbital should be continued in small daily doses for many months after clinical recovery

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DISEASES OF THE PLEURA

Clotted Hemothorax R W Lush J C Nicholson C F Stevenson and W F Nicholson[8] (R A M C) state that of 426 cases of traumatic hemothorax seen in 18 months 44 (10 per cent) were clotted as confirmed at operation Half of the clots were infected There are two types of clotted hemothorax the more common fibrinohemothorax and the rarer type of hematoma Physical signs of fibrinohemothorax are similar to those of fluid In hematoma consolidation is often suggested because the clot conducts sounds from the underlying

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(8) L t 467 470 O t 1944

blood excluding the possibility of inhalation 'blood spots Hemorrhage elsewhere was een in 10 of the 30 cases, in 6 the liver was bruised and in 4 there were hemorrhages on the surface of the heart

[The pos ibility of air embolism as the cause of immediate or early death in the e cases should be considered as indicated in the following article by Gouze and Hayter This mechanism was observed experimentally in dogs by Carlton Rasmu sen and Adams (*Surgery* 17 786 793 June 1945) —Ed]

Air Embolism in Immersion Blast Frank J Gouze and Robert Hayter[6] subjected one guinea pig and nine rabbits to fatal immersion bla t Most animals died in 1–2 minutes one lived 9 and another 40 minutes The typical syndrome consisted of in co ordination collapse gasping bloody froth from nostrils twitching of the extremities and opisthotonos the heart beat 30 seconds after breathing stopped Autopsy revealed lung damage characteristic of blast i e crepitant but very hemor rhagic ti sue Air was found in the circulatory system of eight animals All animals were blasted with their heads uppermost which explains the fact that all eight had air in the brain vessels some had air also in the coronaries and other blood vessels above the heart level Only the rabbit which lived 40 minutes and was carried around in various positions had air also in the inferior vena cava

The findings lead to the conclusion that early death in immersion blast is due to lung damage (hemorrhage and emphysema) which reduces the aeration of the blood, reduces the output of the left ventricle by inter fering with the flow of blood in the pulmonary vessels and causes air embolism Data from autopsies on human victims dying soon after blast would be of great value Since immersion blast and air blast produce identical pulmonary lesions it may be surmised that air embolism can also occur in air blast

For victims of immersion blast the authors suggest compression in an air chamber to reduce the size of or dissolve the air bubbles and administration of oxygen to improve oxygenation of the blood flowing through the

(6) U S Na *M B u 43 871 8 7 Nov mbe 1944*

[Experience during World War II has established the proper treatment of hemothorax with or without clotting of the blood The importance of remov ng the clot and when necessary of decorticating the pleura is paramount f late fibrothorax and permanent functional impairment are to be avoided If the fibrin is not removed extensive calcification of the pleura may occur in subsequent years —Ed]

Hemothorax N P Barrett[9] presents observations based on experience in military hospitals

Failure of the lun to re expand after repeated aspira tion is not due to atelectasis as generally supposed but usually to the fact that the lung is bound down by an envelope of fibrin the deep layer of which is rapidly replaced by fibrous tissue Appearance of fibroblasts early in the investing layer of fibrin is a cardinal point in the pathology of hemothorax It is still a matter of dispute whether the source of bleeding is in the lungs or in the parietes Points pertinent to this subject are presented (1) Though the lung is highly vascular per sistent bleeding from a wound is seldom apparent at operation (2) Persistent bleeding whether serious or slight is generally due to wounds of the chest wall or the diaphragm (3) When the right leaf of the diaphragm has been penetrated by a missile which has passed through the chest blood is apt to be pumped into the chest from the abdomen (4) The intercostal spaces are not invariably safe areas as generally thought A missile pas ing through an intercostal space posteriorly will sever the intercostal vessel between the neck of the rib and its angle there are also a number of vulnerable branches which pa s vertically from one intercostal to its neighbors above and below (5) A foreign body e g a piece of plate glass retained in the chest wall may sever an important vessel and bleeding will start as soon as it is removed (6) Missiles which cause tangential wounds of the chest wall but do not perforate the pleura can induce such commotion in the adjacent lung that pulmonary and intrapleural hemorrhage results (7) A crush injury with or without fracture of the ribs may

(9) L t 1 103 106 J 194

lung In clotted hemothorax however, these signs do not regress but remain remarkably constant When clinical signs suggest hemothorax and aspiration yields little or no fluid clotted hemothorax should be suspected In fibrinohemothorax the roentgenogram characteristically shows multiple fluid loculi although some of the levels are corrugated owing to fibrin floating on the surface of the blood in hematoma it shows a dense opacity extending up toward the axilla which may include areas of translucency due to encysted air and fluid

A few patients may recover spontaneously without operation but this requires prolonged treatment With operation the lungs can expand more rapidly and evacuation of the clot removes an excellent culture medium Risk of infection can be further reduced by chemotherapy Indications for operation are (1) large clot (more than a third of the hemithorax) (2) persistent fever (3) marked loculation in fibrinohemothorax (4) clot with retained foreign body Evacuation of the clot is best combined with decortication i e stripping of the fibrin layer deposited on the surface of the pleura which facilitates inflation of the lung The resulting oozing usually stops after the lung is expanded Positive pressure anesthesia is essential with the pressure recorded manometrically Decortication is easiest between the third and the fourth week when the fibrin layer is firm enough to be grasped by lung forceps but not so adherent as to make separation difficult Earlier operations however should not be avoided for occasionally a simple incision of the fibrin sheath will free the lung After the lung is freed it is expanded by the anesthetist to reveal any fistula which may then be repaired

The authors performed 21 decortications for clotted hemothorax without gross infection and 16 for empyema In the first group there was no fatality and except in one case convalescence was smooth In the patients with empyema several of whom had retained foreign bodies and bronchopleural fistulas results were not so good

involved intercostal internal mammary or large intra thoracic hilar vessels or the vessels of the lung parenchyma Diagnosis of hemothorax is based on the presence of bullet wound or other perforation of the chest wall dulness on percussion shift of tracheal and mediastinal structures absence of breath sounds impaired excursion of the chest wall positive x ray findings and diagnostic aspiration

Small bloody effusions in the pleural cavity are absorbed spontaneously but the larger ones are best handled by slow aspiration or gradual gravity drainage The bloody fluid is not replaced by air In massive organized hemothorax radical management by thoracotomy is the procedure of choice Manual evacuation of the clot and decortication of the lung have proved effective in returning men to duty early and in diminishing incidence of empyema Aspiration is preferred to let alone treatment because morbidity is reduced and complications are avoided or made much le s The object is to reduce the size of the hemothorax and get the lung re expanded as rapidly as possible and to prevent chronic fibrothorax and secondary empyema In performing aspiration it should be borne in mind that the lowest levels at which the needle may be inserted in ent ing the pleural cavity are posterior axillary line at the ninth interspace midaxillary line at the seventh interspace and anterior axillary line at the fifth interspace Aspiration may be necessary at several levels particularly when clotting of blood or formation of fibrin has begun Air replacement is to be avoided because it defeats the objective re expansion of the lung and obliteration of the pleural cavity and prolongs morbidity Aspiration is continued until the patient complains of pain or discomfort in the chest

Injuries to the intercostal vessels give rise to the typical signs of internal hemorrhage and pleural effusion such as increasing pallor restlessness and thirst increasing rate and decreasing volume of pulse falling blood pressure increasing respiratory rate and replace

produce a massive hemothorax on the same or opposite side (8) Extrapleural hematoma is not uncommon

Barrett regards displacement of the mediastinum as a late and indefinite diagnostic sign With a normal pleural cavity outpouring of blood will cause the lung to retract toward the hilus When moderate hemothorax produces a shift of the mediastinum the pleural cavity must have been partially obliterated by previous adhesions To be of diagnostic value x ray examination of the chest must be done with the patient sitting up otherwise the films will show the typical ground glass appearance The earliest symptoms of a large hemothorax are shock pain and dyspnea however the condition may exist without any of these Pyrexia in hemothorax does not necessarily mean infection but the latter should be suspected when fever persists

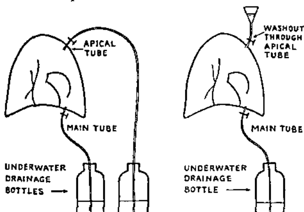
Cases of hemothorax in which bleeding has stopped soon after injury respond rapidly to a few aspirations In massive hemothorax when aspirations do not produce a rapid improvement a thoracoscope should be introduced into the pleural cavity and all the blood clots and fibrin sucked out Cases of hemothorax in which bleeding continues slowly but persistently should be treated by intercostal thoracotomy Treatment for clotted hemothorax is thoracotomy removal of the contents of the pleural cavity and decortication of the lung parietal pleura and diaphragm Thoracotomy is also ideal in hemothorax complicated by retention of a foreign body in the lung

Post Traumatic Hemothorax Management is outlined by Edward M Kent and Harry E Tebrock[1] (M C USNR) The primary causes of early mortality from penetrating chest injuries are disturbances of cardio respiratory physiology and hemorrhage Later death results from combination of the two plus infection Hemorrhage into the pleural cavity occurs in nearly all penetrating wounds of the thorax Any one or a combination of the following thoracic vessels may b

(1) U S Nav M Bull 45 1471 1 1 194

avoidable provided pulmonary expansion is effected and maintained Treatment must start within the first 24 hours and must include good surgery and good aspiration with use of penicillin and special methods when *leakage of air from the lung endangers re expansion* of the lung

In closed pyothorax initial treatment consists of aspiration Aspirations may be necessary daily or on



Fı 1 (l ft) —Tw t b l ft d f h t b th n t d t u l t d bottl

F 18 (ght) —Tw t b l ft pl w h t n p g w th fl l i g n th gh pp tub nd t t u d rw t d b ttl

alternate days and are followed every 48 hours by introduction into the pleural cavity of 50 000 units of penicillin in 2 cc water The factors which prevent this treatment from being completely successful may be clot penicillin resistant organisms rigid lung or rapid production of fluid There is little benefit from aspiration when frank pus has formed It is nevertheless used for a few days to obtain slight initial improvement and to damp down the virulence of the organisms with penicillin At the last aspiration before drainage 20 c poppy seed oil is introduced and roentgenograms taken Operation is done through a small vertical incision just inside the lateral border of the erector spinae The actual

ment of initial pallor by cyanosis In uncontrolled hemorrhage of the intercostal artery ligation should always be done on both sides of the bleeding point before dividing the vessel Injury to the internal mammary artery is always urgent Hemorrhage caused by laceration of the large hilar vessels is rarely amenable to treatment as death occurs rapidly from exsanguination Lacerations of the lung parenchyma are seldom profuse and may be self controlling Hemoptysis is usual in these cases as contrasted to its rare appearance in the aforementioned conditions If bleeding from peripheral lacerations does not stop spontaneously or if it is persistent or massive, an open thoracotomy should be done Incidence of pleural infection from combat wounds depends on the precision of surgical management and judicious use of sulfonamides and penicillin

Management of Traumatic Pyothorax is outlined by J Leigh Collis M H Armstrong Davison and P S Smith (R A M C) based on 44 cases of total or subtotal pyothorax in which the mortality was 27 per cent Cases of early infected hemothorax were excluded The experi

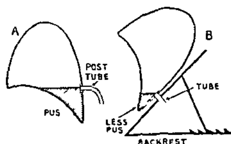


Fig 16—A l te al v w of ch t w th fl nged tube in posit n bov l w t po nt of flu d B h t ly g on the ba k rest

ence in this series led to the conclusion that although localized empyema in war injuries is sometimes unavoidable total pyothorax, with the possible exception of cases associated with esophageal injury or infection with virulent organisms such as hemolytic Clostridium welchii is

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ease and consequently decrease the risk of any type of surgical intervention The evidence that penicillin is a valuable adjunct in treatment of empyema caused by penicillin vulnerable organisms is indisputable Systemic administration of the drug alone sometimes will cause cultures of the fluid to become sterile Intrapleural injections will temporarily sterilize an empyema cavity in most cases However combined systemic and intrapleural treatment is to be preferred for such treatment affects both the pulmonary and the pleural lesions

Penicillin will probably be extremely effective in aborting empyema formation but once pus is formed even if it is sterile and healing by conservative measures is not rapid surgical drainage is mandatory lest chronicity ensue The introduction of penicillin has not altered in any way the fundamental principles of treatment of empyema only the details are changed The authors suggest a tentative plan (1) An intrapleural injection of penicillin is given as soon as infected fluid appears in the pleura local treatment is withheld however until the organism in the fluid is identified An initial positive bacteriologic diagnosis prevents waste of penicillin in infections not responsive to the drug and rules out the possibility of tuberculous effusion or empyema (2) If systemic administration of penicillin has not been employed during the pneumonic stage of the disease it should be combined with local therapy The chief advantage of the systemic route is that the blood will contain a bacteria inhibitory substance which may control a spreading cellulitis or invasive infection The same principle is sound in the management of pneumonia complicated by empyema particularly in cases of streptococcic or staphylococcic empyema (3) Probably three injections of 50 000 units of penicillin on alternate days are sufficient for local treatment Before the penicillin is injected as much pus or infected fluid as possible should be removed by thoracentesis (4) If pus continues to form and thicken surgical drainage should be established A sterile empyema is not a cured empyema and evacua

position of the drain tube is most important It can be seen from Figure 16 that far more efficient drainage is obtained with a posteriorly placed tube Though this method was good in many respects two disadvantages were encountered many patients developed massive collapse of the affected lung and many patients with heavy infection required washing out of the cavities For this reason a second tube was introduced at the time of drainage (Fig 17) This second tube is placed at the extreme apex of the chest close behind the anterior edge of the trapezius muscle When washouts are desired (Fig 18) the tube is occluded by a screw clip and disconnected from the bottle and a funnel is attached A pint of fluid is allowed to run in and the clip closed again The main lower tube is left attached to the underwater bottle The washout fluid (Dakin s solution) enters the pleura and runs out as fast as it flows in

In cases in which there is an opening into the pleura either through a brokendown sucking wound of the chest wall or via a bronchial fistula no useful purpose is served in delaying operation by treatment with aspirations Drainage is instituted immediately along the aforementioned lines but in these cases special problems are met which require modifications of the surgical procedure

Observations on Treatment of Empyema Thoracis with Penicillin are presented by Brian Blades Joseph E Hamilton and David J Dugan[3] (M C A U S) Of 24 patients with empyema 13 received penicillin both systemically and locally 5 intrapleural injections of penicillin alone and 6 only penicillin systemically

From this series it was concluded that the question of adequate drainage and irrigation is most important The prevailing tendency in penicillin treated empyema has been to delay drainage and therefore decrease the chance of premature operations in cases in which the abscess is in a formative stage Moreover use of penicillin will control quickly the pneumonic tage of the dis

(3) Su g ry 17 57 89 Ap l 1945

duct was escaping into the pleural cavity po ibly owing to leakage in a small tributary rather than to rupture of the duct

At no time during the first two weeks of hospitalization was there any infection Subsequently there were an epis de of diar rhea and one of ear infection However seven weeks after admis sion the infant was discharged in normal condition and several months later was in excellent health No cause of the chylothorax was established

[Forbes (*Journal of Pediatrics* 5 191 00 September 1944) also reports a ca e of chylothorax which was bilateral in a 6 week old infant Autopsy did not reveal a cause for the effus on Jahs man (*Annals of Internal Medicine* 21 669 67 October 1944) pre ents a review of th l te ature on chylothorax and comments on its relative rarity —Ed]

Herpes Zoster with Underlying Pleural Rub D C Thursby Pelham and M A Floyer (London) report a case

Woman 46 with a 0 year h story of asthma and bronchitis for 3 days complained of pain in the left side of the chest on deep respiration and coughing On admi ion there were rales over the ent re chest and tenderne s over the seventh and eighth intercostal spaces in the posterior axillary line on the left side no pleural rub was heard Roentgenograms showed chronic bron ch tis but no abnormal ty in the lungs or pleura Four days after admission a small crop of typical vesicles of herpes zoster appeared over the painful area Three days later a pleural fric tion rub directly underly ng the herpes was heard it disappeared *after four days* The pa n *disappeared at the same time* but the vesicles healed slowly with scarr ng n the usual manner No other evidence of pulmona y or pleural involvement was noted

The pleural rub was thought to be caused by herpetic lesions occurring on the surface of the parietal pleura

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PULMONARY EMBOLISM HEMOSIDEROSIS BRONCHIAL VARICES

Pulmonary Embolism Relation of Occlusion of Pulmonary Artery to Sudden Death Results of experi mental studies from the surgical viewpoint reported by Minas Joannides and Arthur L Hesse[6] (Univ of Illi nois) indicated that the body can tolerate a surgical occlusion of the pulmonary circulation up to two thirds of its total volume Occlusion of the pulmonary artery

(5) B t M J 309 S pt 1944
(6) Ill M J 85 79 86 J 1944

tion of frank pus should not be unduly delayed because organisms cannot be found after penicillin treatment has been started

As an adjuvant to skilful surgery, penicillin has already revolutionized management of surgical diseases of the chest There is every reason to predict that with penicillin protection the dangers of operations on the chest will be reduced but the drug will not afford protection from violation of fundamental principles of surgery

[This is a rational and sound consideration of the modern treatment of empyema The possibility of creating a permanent pleural dead space even though this is sterilized by irrigation, should *be stressed Such dead space* unless it *is obliterated by* organization and retraction of surrounding structures becomes filled with transudate which is a permanent menace to the patient It is an avoidable condition —Ed]

Chylothorax in 2 Week Old Infant with Spontaneous Recovery is reported by Morris A Wessel[4] (New York City)

Infant was admitted 24 hours after appearance of signs of acute *respiratory distress and cyanosis There was* no history of trauma or convulsions Breath sounds were absent over the right lung and scattered moist râles were heard over the left lung Fluoroscopy revealed a dense shadow filling the entire right hemithorax with no aeration visible marked shift of the mediastinum to the left and only a small portion of aerated lung visible in the left lower hemithorax. Thoracocentesis of the right pleural cavity yielded 200 cc creamy yellowish fluid and respiratory embarrassment was immediately relieved Roentgenography of the chest showed both lung fields clear the heart slightly to the left and evidence of compression of the right lung field Sulfadiazine was started to prevent pneumonia. In the following ~ weeks thoracocentesis was necessary at 24 hour intervals, after this period it was unnecessary *The aspirated fluid was always* sterile

Vitamin A *absorption test performed on the seventh day of* hospitalization showed a delay of 18 hours vitamin A was found in *the chylous fluid.* Except *for* one day the infant was kept on a low fat and because of loss of protein with each aspiration *of fluid*, high protein formula The amount of fat in the fluid from the pleural cavity during both high and low fat feeding was less than 10 per cent of the dietary fat intake This was assumed to be due to the fact that only part of the absorbed fat and probably of the chylous fluid delivered to the thoracic

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duct was escaping into the pl ural cavity po bly owing to leakage in a small tributary rather than to rupture of the duct

At no time during the first two weeks of hosp talization was there any infection Sub equently ther were an episode of diarrhea and one of ear infection However seven w eks after admission the infant was discharged in normal condition and several months later was in excellent h alth No cause of the chylothorax was established

[Forbes (*Journal of Pediatrics* 5 191 00 Septemb r 1944) also reports a case of chylothorax which was bilateral in a 6 week old infant Autopsy did not reveal a cause for the effusion Jahsman (*Annals of Internal Medicine* 21 663 6 October 1944) pre ents a review of the l terature on chylothorax and comments on its relative rarity —Ed]

Herpes Zoster with Underlying Pleural Rub D C Thursby Pelham and M A Floyer (London) report a case

Woman 46 with a 0 year history of asthma and bronchiti for 3 days complained of pain in the left ide of the chest on deep respiration and coughing On admission there were rale over the entire chest and tenderness over the s venth and eighth intercostal spaces in the posterior axillary line on the left side no pleural rub was heard Roentgenograms showed chronic bronch t s but no abnormal ty in the lungs or pleura Four days after admission a small crop of typ cal vesicles of herpes zoster appeared over the painful area Three days later a pleural friction rub directly underlying the herpes was heard it disappeared after four days The pa n disappeared at the same time but the vesicles healed slowly with scarring in the usual manner No other evidence of pulmonary or pleural involvement was noted

The pleural rub was thought to be caused by herpetic lesions occurring on the surface of the parietal pleura

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PULMONARY EMBOLISM HEMOSIDEROSIS BRONCHIAL VARICES

Pulmonary Embolism Relation of Occlusion of Pulmonary Artery to Sudden Death Results of experimental studies from the surgical viewpoint reported by Minas Joannides and Arthur L Hesse[6] (Univ of Illinois) indicated that the body can tolerate a surgical occlusion of the pulmonary circulation up to two thirds of its total volume Occlusion of the pulmonary artery

(5) B t M J 309 S pt 1944
(6) Ill o M J 85 79 86 J 1944

by thrombosis and embolism was also found to have a quantitative factor Dogs tolerate up to 20 cc of 1 1000 dilution of Monsel's solution of ferric subsulfate in normal saline and up to 10 cc of 1 500 dilution per lb body weight injected intravenously An apparent tolerance was observed after repeated injections of the coagulant and also when it was preceded by the injection of 1 5 cc coramine two to five minutes before operation Tolerance to the presence of coagulants in the blood stream together with increase in coagulation time of the blood in animals which were made to tolerate the injection of coagulants, suggests the possibility of preventing hazards resulting from massive embolism if ways could be found to control the coagulating mechanism of the blood

Surgical occlusion of 50 per cent of the pulmonary circulation is sufficiently tolerated to warrant the possibility of doing pneumonectomy or bilateral lobectomies with comparative impunity, and as long as the lesser circulation is not obstructed up to two thirds of its total no untoward effects should follow However, thrombosis and embolism produce a more complex picture since occlusion or interference with the blood supply of any organ with subsequent infarction, may result Therefore any possible prophylactic measures should be used to prevent formation of thrombi These include avoiding trauma during operation rolling the patient from side to side as soon as he comes out of the anesthetic moving the extremities to prevent stasis of blood, etc When thrombosis is already present embolectomy or ligation of the femoral vein should be considered Conservative measures such as oxygen inhalations intravenous injection of papaverine ½ gr or atropine in doses of 1/150 gr to dislodge a clot from larger into smaller branches and coramine as cardiorespiratory stimulant may be of value

In cases in which death does not occur at once embolectomy by Trendelenburg's technic should be attempted by a skilful thoracic surgeon

Prevention of Pulmonary Embolism Charles A Robinson[7] (Boston) states that it is now generally conceded that pulmonary embolism rarely occurs except in the presence of phlebothrombosis of the deep veins of the lower leg Its prevention therefore resolves itself into prevention of phlebitis Great reduction in mortality would follow recognition of three principles (1) phlebothrombosis usually occurs in a bedridden patient whose venous circulation is retarded and muscle tone relaxed (2) diagnosis is often overlooked if the physician fails to make a daily routine examination of the lower extremities especially of the calves and groin and neglects to note any unexplained rise in temperature and pulse (3) immediate surgical exploration of the veins must be done if phlebothrombosis is diagnosed

Prevention of phlebitis and thus of pulmonary embolism consists mainly in acceleration of venous circulation by suitable exercises begun immediately after the patient takes to his bed Robinson claims good results with routine extension and flexion of the ankles and knees Other means are use of Trendelenburg s position of legs for one hour twice daily nonconstricting abdominal dressings and routine deep breathing exercises Maintenance of fluid balance is vitally important for the dehydrated patient has a slower circulatory rate Varicose veins require ligation division and injection before the fifth month of pregnancy or prior to any elective operation Rough handling of tissues leaning on the patient especially over the femoro iliac region in abdominal operations and poor approximation of tissues are possible contributory factors in failure to establish normal venous return Holding of legs during long gynecologic or obstetric operations is preferable to use of stirrups Patients should be walking after the observation period preceding operation and especially elderly ones be made ambulatory a few days after operation Anticoagulants such as dicoumarin and heparin have not yet proved to be safe in prevention of pulmonary embolism

(7) N w E gl d J M J 231 8 1 8 3 D 1 1944

Ligation of Inferior Vena Cava in Prevention and Treatment of Pulmonary Embolism is discussed by E Everett O Neil[8] (Boston Univ) There are two indications for this operation The first exists when the diagnosis of phlebothrombosis is obvious and the site of the lesion apparent A synchronous propagating thrombosis may occur in both legs the processes extending to the inguinal ligaments or beyond with or without production of pulmonary embolism more frequently phlebothrombosis may occur in one limb and extend to the groin and within a few days the opposite leg may become affected by phlebothrombosis involving the lower leg and thigh The second indication exists when one or more pulmonary emboli have occurred but their source is obscure Pathologic and clinical observations indicate that deep venous thrombosis of the leg plays a major role in production of pulmonary embolism Phlebothrombosis may be quiescent exhibiting no symptoms until death or the first intimation may be signs of pulmonary infarction When the presence of so-called silent thrombosis is suspected the process may exist in one or several groups of deep veins the venous channels of the lower leg, the deep femoral veins the uterine plexus of the female or the prostatic plexus of the male When the source of the embolus is unknown the procedure offering the best guarantee of safety is interruption of the inferior vena cava

Caval ligation was performed in the eight cases, with satisfactory immediate and remote effects In five there had been obvious thrombotic involvement of the lower extremities and in three pulmonary embolism had occurred but no source was evident There were no untoward postoperative effects Minimal discomforts such as heaviness, numbness and moderate swelling of the extremities occurred but were not important enough to interfere with daily activities Edema of the legs is not so frequent or so marked as after division of the femoral vein

(8) New England J Med. 3 641 645 M y 21 194

Formation of Hemosiderin in Lungs George Strassmann[9] (Harvard Univ) reports an experimental study Four hours after homologous blood injected intratracheally enters the pulmonary alveoli of rabbits hypertrophy hyperplasia and desquamation of the alveolar lining cells occur These reactive changes reach their peak in 10 hours and show marked regression at the end of 24 hours The erythrocytes are disposed of rapidly almost entirely by phagocytic activity of the alveolar lining cells Even when an amount of blood equal to the combined weight of the lungs is injected little or no trace of it exists in the lungs when the animal is killed 24 hours later and in normal animals no local formation of hemosiderin is found

Injection of a hypertonic solution of dextrose alone causes transitory pulmonary edema and hyperemia with mild stimulation of the alveolar lining cells and slight exudative reaction in the form of occasional eosinophils When a hypertonic solution of dextrose is combined with homologous blood both the activation of the alveolar lining and the exudative response are more marked than after injection of dextrose or blood alone Many intact erythrocytes are found in the alveoli of animals killed on or after the second day During the second day large amounts of hemosiderin can be seen in both desquamated cells and hypertrophic cells attached to the septal wall By the end of the fourth day most of the intact erythrocytes and wandering macrophages have disappeared The attached alveolar cells although they have been engaged in phagocytic activity and contain hemosiderin may retrogress in size remain in situ and become reactivated by subsequent stimulation as long as 14 days later The hypertrophy and phagocytic activity of alveolar lining cells are thus reversible as long as the cells do not desquamate

Hemosiderin was first observed after 24 hours after 48 hours a positive hemosiderin reaction was obtained in all experiments The appearance of hemosiderin gradu

(9) A h P th 38 6 81 A gu t 1944

ally changed from a diffuse faint, in some instances al most imperceptible blue discoloration of the cytoplasm of the macrophages to a granular aspect and, at the end of a week to small dark compact blue staining masses

[This study of the mechanism of hemosiderosis is of great interest The deposit of hemosiderin in the lungs particularly in cases of congestive heart disease, has been recognized from time to time and among other things, has been of interest in the interpretation of roentgenograms Occasionally it may be the cau e of fine nodular shadows simulating other conditions, such as pneumoconiosis An unusual clinical case with autopsy is re ported and discussed by Douglas Reye (*Medical Journal of Aus tralia* 1 35 37, Jan 13 1945) See also the article by McLaughlin and others this YEAR BOOK p 197 —Ed]

Varices of Bronchial Veins As Source of Hemoptysis in Mitral Stenosis were studied by Frank C Ferguson Richard E Kobilak and John E Deitrick[1] (Cornell Univ) Since bronchial veins are difficult to locate and inject injections were made into pulmonary veins with particulate matter too coarse to enter capillaries

Seven controls without clinical or pathologic signs of mitral stenosis were studied first There were six females and one male aged 26–71 Three had hypertension but only one had terminal cardiac failure Age had no effect on normal capacity of bronchial veins The youngest subject showed the same degree of bronchopulmonary venous anastomoses and the same pattern of submucosal bronchial veins as the older patients Grossly the bron chial veins filled with the injected mass appeared as orange lines in the mucosa of small and medium sized bronchi These veins either formed irregular spider like patterns or had no regular arrangement Few or no ves sels were visible in larger bronchi Many minute injected vessels were seen microscopically in the bronchial sub mucosa Larger vessels were deeper in the submucosa and were well separated from the lumen of the bronchus In spaces between cartilaginous plates there were larger and more deeply placed vessels These seemed to connect bronchial and pulmonary veins In smaller bronchi the submucosa was thinner and veins were more superficially placed Injected material was also seen in veins of the

(1) Am Heart J 28 445 456 October 1944

lung parenchyma It did not appear in pulmonary or bronchial arteries and capillaries The particles of mercuric and lead salts did not enter channels less than 20 microns in diameter

Six nonrheumatic cardiac subjects with cardiac failure aged 39–71 were observed Four had marked hyperten



F 19—L g b b b f g l 16 w th m t l t n d l t d b b l w th m m l f ld v t m tow t h l m fo m g l lat l l t n A d l t d b h l B m al f ld

sion In three veins in the larger bronchi were slightly dilated and definitely more conspicuous than in the previous group

Eleven patients with mitral stenosis aged 16–57 were studied Six showed definite evidence of enlarged bronchial veins Four of the six had greatly dilated bronchial veins along the longitudinal axis of the large bronchi The veins were fairly straight and parallel and seemed to stream toward the main bronchus Figure 19 shows the

large bronchi of a girl aged 16 Large mucosal folds are visible, as well as innumerable dilated veins on the surface of the mucosa Figure 20 shows a section of bronchus from the same subject

The authors believe that in mitral stenosis the flow to the left auricle through pulmonary veins is hindered and pressure in these veins rises above that in the right



FIG 0 —Same ca s p ec ding S ction of la g bronchus show great dil tation of bronch al ve ns a d the r s tuation clo e to lum of bro hus

auricle The blood flow through the anastomosis is reversed and blood passes from pulmonary circulation into bronchial veins and back to the right side of the heart via the azygos hemiazygos and intercostal veins Submucosal bronchial veins leading toward the main bronchi dilate greatly to handle this collateral flow and even become grossly visible The hemoptysis which often accompanies mitral stenosis, yet is not associated with acute pulmonary edema or pulmonary infarction is prob

ably caused by rupture or ulceration of these engorged bronchial veins This hemoptysis resembles massive bleeding from hemorrhoids and esophageal varices which like bronchial veins are submucous shunts between large venous drainage areas A severe coughing spell mild ulcerative bronchitis or a rise in left auricular pressure could initiate such attacks of hemoptysis

[This is a plausible explanation of the mechanism of hemoptysis particularly when sudden and copious in cases of mitral stenosis and other cardiac condition The changes in the bronchial veins probably develop slowly over a period of years since it is uncommon to observe free copious bleeding in early cases —*Ed*]

PNEUMOCONIOSIS

Aluminum Therapy in Silicosis Animal experiments performed by Leroy U Gardner Morris Dworski and Anthony B Delahant (Saranac Lake N Y) verify the general conclusions of Denny Robson and Irwin that aluminum in proper form constitutes an effective inhibitor of quartz in a living host The authors believe that an amorphous hydrate of aluminum possesses certain advantages over the metallic powder used by the Canadian observers The hydrate is stable and does not need to be freshly ground in a mill at the time of inhalation It does not flocculate on contact with body fluids and is therefore more likely to reach all silicotic foci in the lungs Its white color is less objectionable than the coal black of the metallic powder which stains the mouth and face in the present method of administration

In the experiments prolonged exposures far greater than any that might be contemplated for human therapy had no harmful effects on normal animals However such excessive concentrations of aluminum hydrate may unfavorably influence native susceptibility to tuberculosis while the effect is transitory and occurs in only a small proportion of the animals it is sufficiently definite to indicate caution in application of aluminum therapy in man It would probably be unwise for patients show

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ing x ray evidence of any but the oldest and obviously well healed tuberculous lesions

The experiments indicated that successful therapy can be expected only when the inhibitor is administered by inhalation as other procedures do not guarantee the essential intimate contact between quartz and aluminum hydrate Hydrated alumina may be used prophylactically *to prevent development of silicosis, but it should never* become a substitute for accepted methods of dust control As there are always a few persons who respond more rapidly than others to quartz aluminum treatment has a place in selected cases even in the well controlled industry *Inhalation of hydrated alumina as a treatment* for disease already established has been shown to cause retrogression of immature silicotic lesions, its only effect on fully developed fibrous *nodules* is to prevent further enlargement In silicotic animals treatment prolongs life and in men with disability it is said to relieve dyspnea cough and chest pain Probably the most important use of aluminum treatment is for those trained workmen *whose protective mechanism against dust is so subnor*mal that at an early age they begin to show x ray evidence of silicosis even in an environment that is apparently safe for most people By treating such men when x ray first shows evidence of dust reaction their disease *can probably be arrested and the men enabled to con*tinue at their jobs without wage loss

[This represents a conservative view of therapy which is necessary since patients with advanced silicosis may expect too much *Once functional impairment has become pronounced it is doubt*ful whether this or any other form of treatment will have any *material* effect —Ed]

Experimental Silicosis Produced with Ash from Human Silicotic Lungs *Samuel R Haythorn and Fred A Taylor*[3] (Pittsburgh) injected intravenously in experimental animals four samples of ash recovered chemically using pure crystalline silica as control Animals in the control group presented typical lesions including nodules of *the lungs spleen, lymph nodes* peritoneum

(3) Am J Path 21 1 3 145 Janu ry 1945

and blood vessel walls In one rabbit which lived for the 23 months of the experiment there was well developed cirrhosis of the liver Of the rabbits which received lung ash (from a patient who died of bronchiogenic carcinoma) *of which 0 079 per cent was total silica without* free silica all lived throughout the experiment and presented mild lesions of the absorptive type All but one of the animals inoculated with lung ash (from a marble worker with silicotuberculosis) which contained 2 42 per cent total silica and 0 97 per cent free silica lived through the experiment and all showed pronounced absorptive lesions without fibrosis These unanticipated results indicated that the silicates and other contaminating dusts protected the animals from the toxic action of the silica Animals inoculated with suspensions of lung ash (from a patient who died of silicotuberculosis and pneumonia) which contained 1 145 per cent total silica and 0 32 per cent free silica showed progressive granulomatous lesions in peritoneum lymph nodes and spleen Cirrhosis of the liver developed in the only rabbit that lived through the experiment Of the animals inoculated with suspensions of ash (from a patient with massive silicosis) which contained 2 68 per cent total silicates and 1 95 per cent free silica one rabbit and two guinea pigs lived six months or more and all had typical silicotic nodules of the lungs liver spleen and lymph nodes The rabbit presented advanced cirrhosis of the liver and the guinea pigs had calcified granulomas of the peritoneum

Iron Oxide Dust and Lungs of Silver Finishers A I G McLaughlin J L A Grout H J Barrie and H E Harding[4] discuss clinical and radiologic findings in four silver finishers who inhaled the dusts of iron oxide and silver and describe the gross and histologic morbid anatomy and chemical analyses of the lungs in one The x ray examination in these patients revealed stippled or reticulated shadows resembling those found in welders hematite miners and other workers who inhale iron and iron oxide dust These shadows are cast by ag

(4) La 1 1 337 341 M 17 1945

gregation of iron oxide dust opaque to x rays, in the peribronchial and periarterial lymph spaces The presence of silver particles in the lungs does not materially affect this interpretation of the x ray shadows No fibrotic changes (either collagenous or reticular) are set up in the lungs by the inhaled dust which consists mainly of pure iron oxide (rouge, used in the final polishing of silver) Little or no physical disability appears to be caused by presence of iron oxide dust in the lungs although in one case there was emphysema The particles of silver inhaled continually over 40 years produced staining of the elastic tissue in the arterial and alveolar walls In two cases there was slight argyria of the scleras, but in no case was the skin stained with silver In interpretation of the x ray films of the chest of workers in dusty occupations consideration should be given both to activity of the dusts in producing pathologic changes and to opacity of the dusts to x rays A worker who has inhaled radio opaque dusts may present an x ray picture simulating early silicosis miliary tuberculosis or other pathologic condition and yet have no obvious physical disability

[Pendergrass and Leopold (*Journal of the American Medical Association* 127 :01 705 March 24 1945) used the term 'benign pneumonoconiosis' to describe cases of this and other analogous types —Ed]

ASTHMA AND ALLERGIC STATES

Pulmonary Acariasis Possible Cause of Asthma E Soysa and M D S Jayawardena[5] observed a heavy incidence of bronchial asthma among patients admitted to a military hospital in southeast Asia A certain proportion of the patients showed a high degree of eosinophilia ranging from 40 to 80 per cent had no familial or personal history of allergy and did not respond satisfactorily to the conventional therapy of bronchial asthma The present report covers 30 patients from various military units whose ages ranged from 18 to 42 years Only

(5) Brit M J 1 1 6 Jan 6 194

two had a history of previous respiratory ailment Except for two who had had mild attacks of dysentery none of them had a history of any intestinal infestation or of any cutaneous affection associated with eosinophilia Seven had had malaria There was no history of tendency to allergic reaction prior to the onset of asthma which in all but three occurred after enlistment in the Army Twenty five of the 30 patients had been engaged in orderly or sentry duties in ration stores or in loading or transporting rations or had been quartered in the vicinity of ration stores Of the other five three had worked in other dusty stores one was a carpenter and one was a tinker

Onset of the condition was invariably slow and insidious with an intermittent dry cough which became progressively more frequent and troublesome at night Gradually the patients began to experience spells of expiratory dyspnea with wheezing Duration of the asthmatic condition ranged from two weeks to three years The clinical picture on admission was that of the usual symptom complex of asthmatic bronchitis No patient had such allergic manifestations as hay fever urticaria eczema or migraine during hospitalization The total leukocyte count ranged from 10 200 to 37 000 the eosinophil concentration from 33 to 81 per cent There was no appreciable alteration in the total polymorphonuclear or lymphocyte count The erythrocyte count and hemoglobin percentage were generally normal Eosinophilic leukocytes were sometimes observed in the sputum Mites of either tyroglyphus or tarsonemus were found in 11 of the 21 patients whose sputum was examined by the special method described by Carter Wedd and D Abrera Repeated examination of feces showed mild infestation with Ankylostoma duodenale in one case Ascaris lumbricoides in two Trichuris trichiura in three Blastocystis hominis in three and Trichomonas faecalis in one Anthelmintic treatment however produced no reduction in the eosinophil count

Analysis of the roentgen findings before treatment

showed the frequent appearance of a pronounced catarrhal reaction of the finer lung markings resulting in diffuse linear striations evenly and symmetrically distributed in both lung fields which suggested an acute inflammatory process resulting in a bronchitic or bronchiolitic reaction In addition there was a remarkable mottled effect produced by small, discrete ill defined spots disseminated throughout the lung fields, especially in the hilar and basal zones Appearance of the lungs resembled that described as "eosinophil lung" This was more marked in the earlier cases but was evident also in cases of asthma of one to three years' duration Reexamination of the lungs after arsenical treatment showed a remarkable change The nodular opacities causing the mottling had disappeared, and the linear striations had also disappeared or had subsided in intensity Arsenical treatment was given for 6–33 days, two tablets of carbarsone or stovarsol being administered daily re sponse was uniformly good and sometimes dramatic Nine months after the first patient was discharged from the hospital no recurrence of asthma had been reported in any of the patients and several who had been examined showed a normal hematologic picture

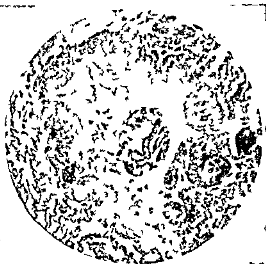
The syndrome apparently corresponds with that described in India as pseudotuberculous condition associated with eosinophilia tropical eosinophilia' "benign eosinophile leukemia and eosinophil lung' Similar cases have been reported from Ceylon and Egypt The syndrome appears to be due in some cases at least to pulmonary acariasis caused by inhalation of a mite laden atmosphere and possibly inducing allergic reactions in the respiratory system The patients in the present series had all lived in mite infested surroundings

Pulmonary Acariasis in Monkeys Recent interest in the possible significance of mites in causation of certain pulmonary disorders such as asthma bronchitis and 'eosinophil lung in the tropics led L J Davis[6] (Univ of Edinburgh) to report observations in a macacus mon

(6) B M J 1 48 Apr 7 1945

key Small nodules scattered through the lungs superficially resembled early tuberculous foci although no other manifestations of tuberculosis were seen Study of some nodules revealed minute arthropods identified as mites probably belonging to the genus pneumonyssus

Walls of the capsules of the nodules (Fig 21) were composed of cellular granulation tissue The capsule



F 1—Nod l in mo k y' l g w th m t t n n l m f p l × 50

lumen was lined with epithelial cells and usually contained an arthropod among the cellular detritus Tissue of the walls consisted of fibroblasts leukocytes eosinophils and plasma and endothelial cells Little formed fibrous tissue and no giant cells were noted A constant feature was heavy pigmentation from granules lying in histiocytic endothelial cells Since the pigment did not give a ferrocyanide reaction and resembled similar pigment in the gut of the parasites it was probably of fecal origin The nodules were usually in close proximity to bronchioles but in no instance was continuity between

a bronchiole and the capsular lumen demonstrated Surrounding lung tissue appeared healthy, although vascular congestion was excessive and erythrocytes were sometimes seen in alveoli

These mites may normally exist as ectoparasites on the host and simian habits would explain how such parasites might be aspirated into air passages In man exposure to environmental conditions resulting in aspiration of extraneous mites might reasonably lead to structural lesions Similar observations on pulmonary acariasis in monkeys reported by others justify further experimental study pending an opportunity to make postmortem studies in man

Physiologically Directed Therapy in Treatment of Intractable Asthma is outlined by Alvan L Barach[7] (Columbia Univ) Studies of pathologic physiology in experimental obstructive dyspnea in dogs have revealed that the elevated negative pressure within the lung during the inspiratory cycle is the critical pathogenic factor responsible for damage of the lungs When the bronchial passageway is obstructed within the chest expiration is prolonged since the intrathoracic bronchi constrict during expiration as volume of the chest is diminished Since constriction of bronchioles is enhanced during expiration the outlet of air from the alveoli is hindered, the alveoli are additionally distended by the succeeding inspiration which puts increased pressure on the pulmonary capillaries and at times results in rupture of their walls In bronchial asthma an increase of pulmonary ventilation brought on either by exercise or by bronchial spasm may result in temporary overdistention of the lung alveoli This functional emphysema may disappear during a remission, but in some patients especially when bronchial infection is present the repeated and prolonged bronchial spasm may result in permanent pulmonary emphysema

In intractable asthma the primary object is to provide repeated bronchial relaxation by the cumulative effect of

(7) Bull N Y A A d Med 0 538 549 Oct 1e

various measures Treatment of status asthmaticus includes use of an oxygen enriched atmosphere to prevent respiratory or cardiac failure during the period in which bronchial relaxation is attempted Inhalation of 50 per cent oxygen in a tent or through a catheter is better than through a mask for asthma patients cannot tolerate a close fitting mask A mixture of 25 per cent oxygen and 75 per cent helium is given preferably in a positive pressure hood for two hours twice daily If the hood is not available the mixture may be given through a mask for three quarters of an hour two or three times daily, with care to maintain an adequate flow to prevent negative pressure within the mask In intractable asthma without anoxia oxygen enriched atmosphere is not necessary

In many patients with intractable asthma aminophylline may be substituted for inhalational therapy Rectal instillation of aminophylline is almost as effective as intravenous administration it does not cause circulatory reactions and may be used at home For rectal use 0 5 0 6 or 0 7 Gm aminophylline powder is dissolved in 20 cc tap water and instilled through a rubber catheter attached to a 20 cc syringe Additional medication includes iodides dilaudid or demerol neosynephrin by nebulization and sodium luminal Intermittent inhalation of helium oxygen mixture may be combined with this regime since it is helpful during the first five days in promoting local bronchial relaxation In patients in whom considerable asthma remains after a week of treatment additional measures such as colonic instillation of ether with equal amounts of olive oil or production of fever with typhoid vaccine may be necessary In patients in whom the relief obtained by bronchial relaxation is only temporary or slight aminophylline may have to be given continuously by mouth or rectum for a long time

Penicillin in Treatment of Intractable Bronchial Asthma Simon S Leopold (Univ of Pennsylvania) and Robert A Cooke[8] (Roosevelt Hosp New York City)

(8) Am J M S 209 784 787 J e 194

present a preliminary report on two patients with intractable bronchial asthma in whom infection seemed to be an important etiologic factor and who received penicillin five and four months previously

CASE 1 —Staphylococcus albus and Streptococcus viridans were recovered from cultures of antral tissue removed at operation The patient received 100 000 units of penicillin daily or a total f 1 3/0 000 units Following treatment there was complete remission of asthmatic symptoms for almost four months, although frequent examination of the lungs during this time revealed the almost constant presence of sibilant rales No such remission occurred in the 15 previous years An acute upper respiratory infection produced recurrence of asthma its subsidence was followed by subjective relief although sibilant rales are usually present

CASE 2 —Streptococcus viridans was recovered from the culture of antral secretion obtained by irrigation The patient received 100 000 units penicillin daily for 10 days At the end of four months there had been no subjective asthma

Penicillin will obviously be of no value in the treatment of asthma due to air borne or ingested substances or of combined extrinsic and intrinsic asthma if the extrinsic factors are not controlled Many young children with allergic inheritance who develop bronchial asthma early in life have *uncomplicated extrinsic asthma* If they continue to have asthma during adolescence and early adult life the perpetuation of their disease may be due to acquired bacterial infection Many of them have then both extrinsic and intrinsic asthma Those individuals who develop bronchial asthma in adult life particularly in the fourth decade or later usually have intrinsic asthma regardless of the family history Penicillin may be of therapeutic value in this group if the organism recovered from bronchial secretions or the upper respiratory tract is sensitive in vitro to penicillin In cases in which infection of the paranasal sinuses has an etiologic relationship to bronchial asthma surgical drainage may be necessary in addition to penicillin therapy to assure lasting relief from asthma

Experience in Care of Asthmatic Patients Undergoing Operation Based on 142 Patients is presented by Louis E Prickman and *Philip D Gelbach*[9] (Mayo

(9) M Clin North America 8 991 1000 J ly 1944

(lime) After a careful allergic survey the patient with allergic asthma who is to be operated on should be placed in a dust free room of constant comfortable temperature and proper humidity in the case of asthma associated with hay fever the room should be pollen free The diet must be bland and minus any food to which the patient is sensitive and the meals should be light Idiosyncrasy to drugs should be investigated In patients with asthmatic bronchitis or with bronchitis complicating allergic asthma cough expectoration and wheezing should be controlled by a period of preoperative rest until inflammation subsides Medication includes expectorants especially iodides and epinephrine ephedrine neosynephrin or propadrine hydrochloride is used continuously to forestall hard cough and a severe asthmatic paroxysm Infected sinuses should be drained The degree of emphysema must be determined by x rays for marked emphysema contraindicates surgery Underlying bronchitis is usually the cause of asthma in elderly people the combination of age and bronchitis increase operative risk When the cough subsides when the patient can lie flat on his back all night and when there has been no recent acute respiratory infection necessary operations may be considered

When pulmonary complications develop postoperatively they must be recognized and treated early Important precautionary measures are inhalation of oxygen or helium and oxygen brief hourly inhalations of carbon dioxide to combat atelectasis and rolling the patient from side to side Frequent subcutaneous injections of 6 minims of epinephrine supplemented by intravenous or rectal use of aminophylline will usually control asthma Chemotherapy should in some instances be given pre and postoperatively

Of the 142 patients in this study 102 had asthmatic bronchitis 32 allergic bronchitis and 8 mixed asthma Twenty two had postoperative pulmonary complications six pneumonia six atelectasis six bronchitis and four severe asthma Pulmonary complications developed in 24 ; ~f patients with upper abdominal operations

and in 13 per cent with lower abdominal operations Therefore in asthma biliary tract or stomach operations should be well considered from all standpoints The mortality from postoperative pulmonary complications was 1 4 per cent Spinal or intravenous anesthesia was the method of choice in asthmatic bronchitis Of 58 patients given ether 10 developed pulmonary complications

Spontaneous Pneumothorax and Bronchial Asthma A case is reported by Hugo T Engelhardt and Vincent J Derbes[1] (Tulane Univ)

Man 48 on admission complained of dyspnea which developed suddenly three weeks previously He had had a chronic productive cough for 20 years Three or four attacks of asthma occurred following pneumonia 1½ year before admission Respirations numbered 46 and were shallow and labored, pulse rate was 140 and temperature normal There were hyperresonance diminished tactile fremitus and diminished breath sounds over the right lung and moist rales over the lower halves of both lungs Heart and trachea were displaced to the left Ankles and feet showed pitted edema A chest roentgenogram revealed 50 per cent collapse of the right lung Thoracocentesis yielded 900 cc air Two days after admission a blowing sound heard over the right chest suggested bronchopleural fistula Despite repeated aspirations he died four days after admission

Autopsy disclosed a small right lung its surface marked by fibrous adhesions and occasional emphysematous blebs At the apex some of these blebs were collapsed The cut surface had a mottled appearance The alveoli were partially collapsed and contained pigment bearing macrophages in a few areas the alveoli were dilated and had thin ruptured walls All the bronchi were dilated There was no gross or microscopic evidence of tuberculosis The pleura was thickened by dense scar tissue and fibrosis

Pneumothorax should be suspected when asthma patients complain of sudden pain in the chest with or without dyspnea Prognosis is usually good Aspiration is contraindicated for three reasons (1) the equality of pressure within and without the alveolus facilitates healing of the torn valve vesicle (2) removal of air and subsequent negative intrapleural pressure favors formation of bronchopleural fistula which in turn (3) favors infection of the pleural space Tension pneumothorax is the only indication for aspiration Otherwise treatment

(1) Ann I t Med 1 711 717 O tober 1944

consists of bed rest and sedation and after the site of pleural rupture has healed administration of pure oxygen

[The administration of oxygen e ther by inhalation or by pleural insufflation to hasten re expansion of the lung is seldom if ever necessary or advantageous —Ed]

Serial Roentgenograms of Chest in Periarteritis Nodosa As an Aid to Diagnosis Clinical and experi mental evidence shows that periarteritis nodosa repre sents an extreme hyperergic response of the vascular system Besides foreign serums and sulfonamides many other types of sensitizing antigens may produce this con dition e g bacteria or their products A critical study of the literature shows that pulmonary changes are by no means rare in this disease A Elkeles and L E Glynn report two cases to demonstrate that serial x rays of the chest may be of assistance in diagnosis One case is cited here

Woman 4 complained of cough pain in the chest and gen eral weakness of two years duration and pain in the feet of two weeks duration Chest examination revealed slightly dimin shed movement at the apex but no other abnormal phys cal s gn The cardiovascular system was normal No tubercle bacilli were found in the sputum The blood picture showed 10 per cent eos n ophils A chest x ray on admission (F g) showed increas d d nse hilar shadows and nonhomogeneous opacities in both upper lobes with interconnecting streaks toward the upper gments of the hilus The vascular markings were pronounced particularly in the lower zones A second x ray film taken approximately seven weeks later (Fig 3) showed a de rea e in the hilar sha l ows the opacit es in both upper lobes had d appeared and the lung fields were clear About six weeks late a roentgenogram showed again an enlarged rregular hilar shadow and increased dens ty and diffuse mottling of th lower lung fields most ma ked at th bases and near the hilar region (Fig °4) During her illness the pat ent had two ep sodes of urticar al rash In the later stages of the disea e the chest x rays showed some enlargement of the heart pa t cula ly noticeable in the pulmonary conus and artery which may have been caused by widespread involvement of the pulmonary vessels Gradually a marked hilar fibrosis developed. Pleural effusion first formed at the base f the left lung and shortly before death it was bilateral

The characteristic x ray features of the lungs in this case were transitory infiltration and persistent and pro

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gressive involvement of the pulmonary vessels associated with mesenchymal structural changes, mainly in the hilar regions and bases Autopsy confirmed the clinical findings

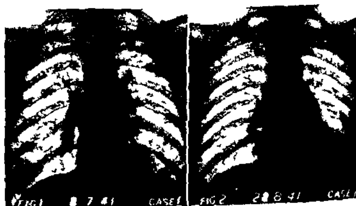


Fig 22 (l ft) —July 8 1941
Fig 3 (ight) —S me case Aug 28 1941

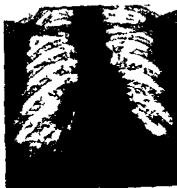


Fig 4—S me a O t 8 1941

[These cases would have to be distinguished roentgenographically from tuberculosis sarcoidosis metastatic malignant disease pneumoconiosis and other conditions —Ed]

NEOPLASMS

Bronchiolar Origin of Alveolar Cell Tumor of the Lung According to Peter A Herbut[3] (Jefferson Med College Hosp) alveolar cell tumors are so typically epithelial that most authors have called them carcinomas The most obvious explanation would be that they originate from septal cells except that the genesis of septal cells is still a moot question Since the concept of mesenchymal origin is gaining more and more advocates it is difficult to conceive that a mesenchymal cell gives rise to a typical carcinoma Authors who consider the alveolar cell tumor a separate entity point to the frequency with which regenerated alveolar epithelium is found in chronic inflammatory and fibrotic processes of the lungs They further state that these regenerated cells arise from septal cells and that sometimes regeneration proceeds so far that the process might even be considered cancerous

Although Herbut concedes that alveolar cell tumor and regenerated alveolar epithelium have a common origin and that the former might even be preceded by the latter he found no convincing evidence that the septal cell is the parent cell A detailed histologic review of 60 bronchiectatic lungs and of lungs from patients with tuberculosis organizing pneumonia interstitial pneumonia and lipoid pneumonia revealed several findings all pointing to an origin of regenerated alveolar epithelium from the basal cells of the bronchiolar mucosa focal proliferations of the basal cells of the bronchi and bronchioles with extension into surrounding tissues their direct linear continuations with the regenerated alveolar epithelium identical morphologic appearance of the two types of cells failure to demonstrate satisfactory transitions between regenerated cells and alveolar phagocytes on one hand and the normal inner surface of the septums on the other and absence of phagocytosis by the regenerated epithelium On this basis Herbut holds that alveolar cell tumors likewise arise from the

(3) Am J P th 20 911 9 9 S pt mb 1944

basal cells of the bronchioles and not from septal cells He presents six cases of primary carcinoma of the lung of which three meet all criteria of an alveolar cell tumor and three are typical bronchiogenic carcinomas with some areas which microscopically are indistinguishable from areas in alveolar cell tumors

From his study, Herbut concludes that the parent cell in all cases of primary carcinoma of the lung is the basal cell of the bronchial or bronchiolar mucosa Distribution of the subsequent tumor depends on the further differentiation of the cells If they are anaplastic or squamous they will be irregularly distributed throughout the lungs or will occupy the alveolar spaces just as does an inflammatory exudate in pneumonia If they are cuboidal or columnar they will line the septums producing the well known alveolar arrangement Whereas few tumors are distinctly of one group or the other, there are many intermediary transitions between the two

[This is an instructive study and conception of this type of malignant dis ase Among other recent reports on the same subject is one by Ikeda (*American Journal of Clinical Pathology* 1. .0 62 February 194) The roentgen and pathologic aspects have been discu sed by Geever Carter Neubuerger and Schmidt (*Radiology* 44 319 3.4 April 1945) The resemblance of the disease to adenomatosis (Jaagsiekte) in sheep was again pointed out by Bonne (*American Journal of Cancer* .. 491 501, April 1939) —Ed]

Present Status of Surgical Treatment of Primary Carcinoma of the Lung William Francis Rienhoff, Jr[4] (Johns Hopkins Univ) reviews 181 consecutive cases of primary carcinoma of the lung seen during an 11 year period of these 110 (61 per cent) were inoperable at the time of exploration Ratio of males to females was 6 1 *The oldest patient was 69 the youngest 19* Age is no contraindication to operation Cough was the chief symptom in 71 per cent of patients If the type of cough in an adult chronic cougher' becomes spasmodic productive or nocturnal, or if a person who has heretofore coughed infrequently suddenly has a constant hacking cough, attention should be focused on the bronchial tree and bronchial neoplasm suspected Hemoptysis was as

(4) J A M A 1 6 11 311 8 D 30 1944

sociated with cough in 63 per cent copious hemoptysis was usually associated with the adenocarcinoma type of intrabronchial tumor Tuberculosis and carcinoma coexisted in two cases Pain a complaint in 50 per cent does not depend on respiration as in pleuritis it is most frequently described as a dull ache deep in the chest Persistent pain in the chest without inflammatory signs or a history of aspiration of a foreign body is suggestive of pulmonary neoplasm Pain down the arm or in the chest wall characteristic of the superior sulcus or Pancoast tumor is caused by direct invasion of the ribs or brachial plexus or both Hyperpnea which occurred in 23 per cent may possibly be caused by a plug of mucus occluding a secondary or tertiary bronchus already partly plugged by an intrabronchial tumor the bronchopulmonary segment of lung to which the occluded bronchus is a tributary thus becoming the site of obstructive emphysema Many patients had recently had numerous attacks of pneumonia These attacks had no seasonal incidence

Chest roentgenograms were positive in every instance An infiltrating hilar shadow in a patient past middle age associated with cough hemoptysis and absence of tubercle bacilli in sputum almost certainly indicates a bronchiogenic carcinoma The roentgen shadow may be produced by the tumor itself or by atelectasis bronchiectasis pneumonitis or abscess caused by occlusion by the tumor of a bronchus leading to a bronchopulmonary segment or segments Second in importance for diagnosis is bronchoscopy In 61 per cent the carcinoma was seen and the diagnosis confirmed by biopsy in 39 per cent bronchoscopy was negative Even if the growth cannot be seen bronchoscopy may reveal fixation deformity due to pressure of a portion of the bronchial tree or occlusion of a bronchus by a small growth not visible roentgenographically Biopsy specimens should not be removed by aspiration because of danger of implantation of cancer cells or infection If a definite diagnosis cannot be made thoracotomy should be performed

it once No complications followed thoracotomy in 25 patients in whom it was done

Clinical course depends on whether the tumor is intra or extrabronchial the former produces symptoms much earlier than the latter Extrabronchial tumors may interfere with venous return from the neck by involvement of the superior vena cava on the right, or laryngeal palsy or Horner's syndrome on the left Tumors arising in the periphery are asymptomatic In 70 per cent of the 71 patients who underwent total pneumonectomy there were metastases to the bronchial and tracheal nodes, emphasizing the necessity of total pneumonectomy with dissection of these nodes In the other 110 cases, metastases also involved in order of frequency, the supraclavicular and axillary nodes liver pleura, pericardium heart contralateral lung osseous tissue, brain, skin and subcutaneous tissue Histologically the tumors belonged to two groups the flat and squamous type (64 per cent) or the adenocarcinoma (36 per cent) In the latter were included the adenocarcinomas the oat cell types and cylindric cell carcinomas Of the patients still living 63 per cent had the flat squamous type and 37 per cent had adenocarcinoma

The only efficacious method of treatment of pulmonary carcinoma is total pneumonectomy with removal of regional lymph nodes radiation is of no benefit The lung is easier to operate on than any other organ except the breast Surgical removal is likely to be successful because of the slow growth and spread of these tumors Furthermore the remarkable ability of the contralateral lung to undergo compensatory changes prevents incapacitation of the patient

The immediate mortality in the 71 patents undergoing surgery was 21 per cent 7 of the 15 deaths were due to complications unrelated to the operative procedure More recently perfection of anesthesia and use of sulfonamides and penicillin have greatly added to the safety of the procedure Thirty five per cent of the patients are still alive, one for 11 years one 9 y

years and one 4 years Nineteen others are surviving for periods from one month to three years Thirty-one pa tients (44 per cent) lived for one month to five years after discharge Most patients were definitely benefited by the operation

[Rienoff does not mention the asthmat or asthmatoid wheeze particularly when unilateral as an rly and important diagnostic symptom and sign of cancer The patient should always be ques tioned concerning this —Ed]

Severe Asthmatic Dyspnea As the Sole Presenting Symptom of Generalized Endolymphatic Carcinomatosis Albert I Mendeloff (Harvard Univ) reports two cases in which pulmonary metastases from intra abdomi nal cancer gave rise to a clinical syndrome so typical that therapeutic regimes routine for that syndrome were instituted without suspicion of the underlying malig nant process In both cases the syndrome was asthmatic dyspnea and the underlying pathologic process pulmo nary endolymphatic carcinomatosis In neither case were there any signs or symptoms referable to the primary site of the tumor nor did clinical and roentgenologic in vestigation disclose any evidence of metastases to other organs

Review of the literature discloses that the respiratory symptoms in cases of carcinomatous lymphangitis of the lungs depend primarily on whether the tumor cells have obstructed the smaller pulmonary arterioles to a degree sufficient to cause pulmonary hypertension in which type symptoms and signs of right sided heart failure may be the presenting features or whether the infiltration is pre dominantly endolymphatic and peribronchiolar as in the present cases with the symptoms more strictly ref erable to interference with respiratory exchange and with normal activity of bronchial musculature The syn drome should be suspected in any patient young or old in whom there develops either suddenly or insidiously a rapidly progressing tachypnea associated with cough occasionally cyanosis and sometimes pleuritic pain Signs of right sided heart failure may be found In most cases

1 A n I t Med 3 39 M h 194

other evidences of malignancy may be elicited, but a small number of patients present only a severe dyspnea with or without wheezing Assman first described the roentgen picture of endolymphatic carcinomatosis as characterized by a pattern of thin lines extending from the hilus toward the periphery with frequent reticulation The hilar nodes are usually enlarged Unless actual nodules are present the picture is more often suggestive than diagnostic Similar findings may be observed in pneumoconiosis, miliary tuberculosis, lymphoma and postinfectious fibrosis

[A good report on the roentgen appearance and pathologic changes of this type of metastatic carcinoma in the lungs is presented by Mueller and Sniffen (*American Journal of Roentgenology and Radium Therapy* 53 109 128 February 1945) —Ed]

Pulmonary Metastasis of Carcinoma Diagnosed by Bronchoscopy In recent years thoracic surgery has developed to such an extent that it has become relatively safe to perform pneumonectomy for removal of primary tumors of the lung It is therefore essential that primary tumors be distinguished from metastases The most important criterion is believed to be presence or absence of bronchial obstruction However it is erroneous to believe that metastatic lesions never involve the bronchi Large metastatic tumors of the parenchyma may extend directly into the wall of the bronchus and ulcerate through the mucosa or the bronchial mucosa may be the site of direct metastasis In either case the intrabronchial lesion may become large enough to obstruct the bronchus completely and cause atelectasis [more often pneumonia —Ed] of that portion of the lung distal to the obstruction As a result the clinical signs and symptoms and the roentgen findings may be indistinguishable from those produced by primary bronchiogenic carcinoma William S Tinney and John R McDonald[6] (Mayo Clinic) present three cases in which a metastatic lesion involving the mucosa of the tracheobronchial tree was seen through the bronchoscope In Case 1 there was a direct invasion of the trachea by carcinoma of the thy

(6) Minnesota Med 8 4 3 8 July 194





F G (l ft) —C 3 Hyp ph m f k d ey
FIG 6 (ht) —S m p pull ry typ m





FI 7 (l ft) — m m t t t b h m f l g l g l g

FI 8 (r ht) —S m h t f l ng k d y (F b) f t ll d t l w th

roid Case 2 was an example of carcinoma of the breast with metastasis to the bronchial mucosa

CASE 3—Woman 30 was admitted because of hematuria of nine months' duration Clinical diagnosis of a neoplasm of the right kidney was made and nephrectomy performed Histologic examination revealed hypernephroma (Figs 25 and 26) The patient remained asymptomatic for two years then began to complain of pain in the right thorax progressive nocturnal dyspnea cough and hemoptysis On bronchoscopic examination a large tumor was found in the left upper lobe bronchus Biopsy of this lesion revealed hypernephroma which demonstrated similar morphologic characteristics to those seen in the kidney Left pneumonectomy was performed Surrounding all the major bronchi and vessels of the lung was a grayish tumor mass measuring 3.5 × 4 × 3.5 cm (Fig 27) There was involvement of the peribronchial lymph nodes The entire lung showed marked atelectasis Microscopically this neoplasm was composed of hyperchromic cells arranged in a separate formation similar to that seen in the kidney (Fig 28) The patient was last seen more than four years after operation, and there was no evidence of further metastasis or of recurrence of the tumor

[The airways may also be invaded by cancer arising in contiguous structures such as the esophagus —Ed]

Intrathoracic Mediastinal Lipoma A case is reported by Thomas B Wiper and Joseph M Miller[7] (M C A U S)

Soldier 46 complained of dyspnea and palpitation on exertion Examination revealed flatness of the left base without fremitus decreased breath sounds which angled off into the left axilla and absence of the apex impulse with increased dulness of the cardiac area The roentgenogram showed a large soft tissue mass occupying the lower left lung field and displacing the heart and mediastinum to the right (Fig 29) The left pleural cavity was aspirated but no fluid was obtained Combined roentgenographic bronchographic and bronchoscopic interpretation led to the conclusion that the patient had a mass in the left mediastinum which produced compression of the left lower lobe and indentation of the left lateral wall of the lower portion of the trachea about 1.5 cm above the carina X ray films after introduction of air into the left pleural space showed the tumor to be extrapleural and extrapulmonary

On operation the left lower hemithorax was found to be filled with an encapsulated fatty tumor the size of a football lying between pleura and pericardium completely occupying the anterior mediastinum and encroaching on the normal lung position The capsule was incised and the tumor enucleated en masse

(7) Am J Surg 66 90 9r Oct 1944

De pite thorough hemostasis 700 cc sanguineous fluid had to be remove l from the left pleural cavity on the fourth postoperative day On the fifteenth day thrombophlebitis of the left arm ap

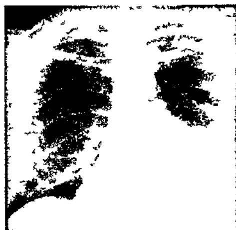


Fig 29 —Film f h t n up ght p t

peared Except for these two episod s recovery was uneventful The electrocard ogram which showed some changes after op ra tion later became normal

THE PNEUMONIAS LUNG ABSCESS

Revaluation of Pneumonias in Infancy According to John M Adams[8] (Univ of Minnesota) the aspiration or gravitation of bacteria laden fluid from the upper respiratory tract beyond the epiglottic barrier is now considered more important in causation of pneumonia in infants than inhalation of infected droplets from the atmosphere However the latter factor seems to be op erative in influenza common cold measles and probably many atypical pneumonias Air borne infections are pre disposing illnesses which greatly increase the activity of the potential pathogens frequently resident in the upper respiratory tract The usual primary pneumococcic pneu monias types I II and VII are relatively rare in in

(8) J P diat 25 369 385 N mbe 1944

fancy, most pneumonias are secondary or complicating *infections* Probably a large group of pneumonias are caused by two or more agents acting synergistically or in concert This concept of dual or multiple etiology is particularly significant in both prevention and management of these cases Preventive measures include the isolation of infants with precursor diseases to avoid further

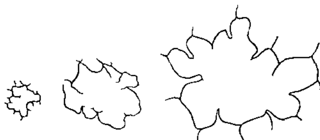


FIG 30—Infant 6 m th p ne pos t n f postu l d a n ge Bed el v ted t f t about 1 degrees

bacterial contact early recognition of the bacteria involved and treatment with a corresponding chemotherapeutic agent

Realization of the etiologic importance of aspiration or gravitation of bacteria laden fluid into the lung in infantile pneumonia led to some practical preventive measures Much can be accomplished by proper posture alone The backward slope of the trachea and bronchi is an important anatomic factor Placing the infant on his abdomen produces an angle of 20 degrees between the trachea and the main bronchi By elevating the foot of the crib the angle between the pulmonary passages and the horizontal plane can be increased by 10–15 degrees The prone position is well tolerated by babies and many seem to prefer it The mattress under the infant should be firm and flat *allowing free movement of the head* (Fig 30)

In infants the structures involved in removing material from the lung are immature and less efficient than those in the adult In infants the development of cilia may be incomplete or absent in bronchioles 0 75 mm or less in diameter whereas in the adult lung ciliated cuboidal epithelium is found in bronchioles 0 35 mm in diameter Neonatal asphyxia produces pulmonary congestion and edema and depresses the respiratory center and may therefore become a factor in causing congenital



F 31 (l ft) —Th d fig 3 1 33 ll t t h g n i f s cul g f m gr wth nd d t vity f l g F m h ld 9 w k ld

F 3 3 (e te) —F m yo th 14 y

Fig 33 (ght) —F om dult 38 (F m Mill Th Lu g (Sp gfi ld Ill Ch l C Thom s, P bl h 1937))

aspiration pneumonia Postural drainage and use of oxygen are essential in the treatment of asphyxia The problem of sudden death in infants (crib death) is not yet solved but cases have been reported indicating that pneumonia may be responsible

Adams presents an etiologic and pathogenic grouping of pneumonias of infancy and describes their predominating histologic features Aspiration pneumonia was reported by Pinkerton in six patients after aspiration of lipoids Fat laden macrophages and giant cells were found by Ikeda in pneumonias resulting from aspiration of oils *Vernix membrane and amniotic debris were found* by MacGregor in congenital aspiration pneumonia Tuberculous pneumonia caused by primary invasion of the tubercle bacillus into the lung produces lesions characterized by epithelioid and typical giant cells Botsztejn

reported five cases of eosinophilic pneumonia in infants Fits of coughing severe dyspnea, pleurisy complicating hilar pneumonia, afebrility and subacute course were the presenting symptoms Primary and secondary bacterial pneumonias produce a varied picture Staphylococcic pneumonia produces clustered abscesses, influenza bacillus bronchiolitis *pneumococcus diffuse and* localized consolidations hemolytic streptococcus distention of interstitial lymphatics with focal and diffuse consolidations Interstitial pneumonia (often due to action of a virus and a bacterium) shows bronchiolitis and peribronchiolitis thickening of interlobular and alveolar septums and infiltration by plasma cells and lymphocytes

Primary virus pneumonitis of infants shows necrosis ulceration and proliferation of bronchial epithelium The specific distinguishing feature in these cases is the presence of cytoplasmic inclusion bodies in the epithelium of the bronchial peribronchial and alveolar tissues Secondary virus pneumonia (Goodpasture) following measles or whooping cough, produces hemorrhage around areas of inflammatory consolidation, stringy mucous exudate ulcerated lesions in the trachea scattered necrosis of the mucous glands and intranuclear inclusions in epithelial cells In syphilitic pneumonia, the lungs are pale and there is extensive hyperplasia of the fibrous elements of the interalveolar tissue Vitamin A deficiency produces metaplasia of the epithelial linings of the pulmonary system which probably prepares the way for invasion of secondary pyogenic organisms and thus explains the frequency and severity of pneumonia in infants with such avitaminosis

Adams describes a recent epidemic of thrush pneumonia in eight infants Monilia albicans rarely produces pneumonia Excessive mucus in the mouth and throat was seen in all these patients in contrast with the dry mucous membranes in cases of ordinary thrush Roentgen changes in the lungs consisted of a diffuse type of central infiltration *Six babies had impetigo at the* time of onset of lesions in the mouth One [illegible] d

and autopsy revealed staphylococcic pneumonia indicating that Monilia albicans and staphylococcus played a synergistic role in this unusual epidemic

[An understanding of the factors which contribute to the cau e and protract on of pneumonias in nfancy will enable the clinician to institute preventive measures and often to shorten the cours of a disease which otherwise may eventuate in later years in chronic cond t ons such as bron h ectasis —Ed.]

Pulmonary Changes in Chronic Cystic Pancreatic Disease are described by George J Baylin[9] (Duke



F 34 —Typ c l di t b t f l s w th p d min t ch g i th d f lu g

Univ) Chronic cystic fibrosis of the pancreas has been established as a disease entity In most cases the patient is an infant who dies of bronchopneumonia or other pulmonary lesion before the age of 6 months The usual history includes frequent colds and failure to gain weight There are occasional diarrhea and foul stools but since the pulmonary syndrome is most prominent the underlying disease is apt to be unrecognized A low vitamin A absorption and steatorrhea are constant find

(9) Am J R ntg l 5 303 306 Septembe 1944

ings The most reliable diagnostic procedure is an assay of pancreatic enzymes, absence of trypsin and lipase in duodenal contents is absolute evidence of pancreatic deficiency Prognosis is poor, most information has been derived from autopsies However, in some instances supportive and vitamin therapy have resulted in at least *temporary improvement*

Since vitamin A deficiency is always present consequent epithelial damage in the lungs leads to infection Pulmonary changes are therefore most marked wherever there is a greater abundance of epithelium The roentgen picture is consistently that of marked involvement of the hilar region characterized by areas of increased mottling and densities Toward the periphery there are less marked streaking and mottling Since the pancreatic deficiency is the underlying cause of these changes they *are progressive if the pancreatic disease persists* Atelectasis is sometimes present and bronchiectasis is frequent as result of epithelial damage and infection Andersen holds that any infant having bronchiectasis should be examined for possible pancreatic disease (Fig 34) Another roentgen aspect of cystic fibrosis of the pancreas concerns the secondary changes in the intestinal tract such as hypomotility associated with some dilatation of the small intestine Any infant who shows the aforementioned lung changes and fails to improve with usual methods of treatment should be suspected of having cystic pancreatic disease

Studies on Primary Pneumonia Clinical Features and Results of Laboratory Investigations Edward C Curnen George S Mirick James E Ziegler, Jr Lewis Thomas and Frank L Horsfall Jr [1] (Hosp of the Rockefeller Inst) studied 106 patients with primary atypical pneumonia (95 males and 11 females) all were young adults The clinical features most helpful in diagnosis were gradual onset of malaise, cough headache and fever lack of respiratory distress relative bradycardia normal leukocyte count and a paucity of pulmonary

(1) J Cl Inve t g t n 24 09 r M h 1945

signs on physical examination despite x ray evidence of pneumonia The site of pulmonary consolidation was most frequently in the lower lobes and the incidence of involvement was almost identical on the two sides More than one lobe was involved in 58 patients two were involved in 38 three in 8 four in 4 and all five in 6

The x ray shadow frequently was diffuse and radiated from the hilus but sometimes it assumed a variety of patterns and at times was undistinguishable from that observed in other pneumonias bronchiectasis and tuberculosis Duration of illness should be considered in interpreting x ray films and the rate of clearing is of particular value in excluding chronic pulmonary disease Resolution of the consolidated areas proceeded from the periphery of the lung toward the hilus in most cases of atypical pneumonia but occasionally this was reversed Frequently after all parenchymal involvement seemed to have disappeared the bronchovascular markings remained prominent Complete clearance was noted in half the patients at the end of the second week of illness and in 80 per cent by the end of the third week

Chloride balance studies showed no striking disturbance of chloride metabolism and plasma alpha amino acid levels were found to be within the normal range in contrast to pneumococcic pneumonia in which the chloride metabolism is usually disturbed and the plasma alpha amino acid levels are significantly reduced

Serums obtained from 64 patients throughout the course of the disease were tested for cold hemagglutinins against human group O erythrocytes only 18 5 per cent showed this property

By appropriate technics pneumococci can frequently be isolated in cases of atypical pneumonia but it is unusual to find them by direct examination of sputum using the quellung technic In no case was there evidence that any of the bacterial species isolated by routine methods was casually related to the disease However in certain cases it may be impossible to determine whether or not the pneumococci or hemolytic streptococci

isolated from such a patient are implicated in the pathogenesis of the illness under such circumstances an adequate trial of sulfonamide therapy is indicated A nonhemolytic streptococcus designated as streptococcus MG was isolated from sputum or nasopharyngeal cultures of 45 of the 106 patients In some instances this streptococcus was cultured directly from the throat or from fresh sputum It was also cultured however, from source materials which had been stored at —70 C for periods varying from a few weeks to more than a year

Virus studies revealed that neither Rickettsia diaporica nor the psittacosis group of viruses was responsible for the disease A filtrable virus recovered from patients with primary atypical pneumonia was found to be transmissible on intranasal inoculation to young guinea pigs and cotton rats Results of neutralization tests with human serums were inconclusive Guinea pigs frequently developed lung lesions after intranasal inoculation with broth and one agent was recovered by intranasal passage in guinea pigs which produced pulmonary consolidation in cotton rats and hamsters and resembled an agent obtained from normal hamsters The significance of any of these viruses in the pathogenesis of primary atypical pneumonia remains to be determined

Primary Atypical Pneumonia of Unknown Cause with Unusual Manifestations and Complications Robert E Glendy Samuel B Beaser and Walter D Hankins (M C A U S) report unusual manifestations occurring in 150 cases of atypical pneumonia at an army station hospital meningismus occurred in 3 cases pleural effusion in 4 marked leukopenia in 1 pulmonary abscess in 4 and late secondary infection in 2

Complaints referable to the central nervous system were stiffness of the neck headache, disorientation vertigo and strabismus The patients with pleural effusion were all moderately or severely ill in all the fluid absorbed slowly without paracentesis Relapse or spread of the parenchymal infection was likely especially when

(2) A ch I t M & 5 30 38 5 n 1945

the patients became ambulatory too soon Remarkable features of one case were leukopenia and marked out pouring of immature cells prompt return of blood pic ture to normal coincided with defervescence A note worthy feature of the three cases of aputrid pulmonary abscess was the resemblance of the condition to tubercu lous cavitation especially when the process was located in the upper pulmonary fields This condition seems to result from secondary infection during convalescence from atypical pneumonia Such superinfections in con trast with the primary disease are accompanied by leukocytosis Sulfonamides are as effective in treatment of such infections as in treatment of primary bacterial infections in contrast with their ineffectiveness in pri mary atypical pneumonia The course of such aputrid abscesses is benign and surgical intervention should be withheld in favor of conservative therapy The one fatal ity occurred in a case of primary atypical pneumonia of great severity and superimposed secondary infection in the form of a pulmonary abscess and empyema at a time when the patient was debilifated though recovering from the primary disease Two patients had fever leuko-cytosis and spread of pneumonia late in convalescence both promptly responded to sulfonamides

Routine use of full doses of sulfonamides from the onset of primary atypical pneumonia does not seem jus tified since complications due to these drugs are more frequent and more dangerous than secondary bacterial complications It is suggested however that the drug be given after the first week in small nontoxic doses

[The nature of rarefied shadows n the roentgenogram in cases of primary atypical pneumonia is not entirely clear although they sometimes suggest abscess In some or perhaps most of these situations the shadow may epresent bullous emphysema produced by a check valve mechanism t may disappear w th n a few days —Ed.]

Cold Hemagglutination in Primary Atypical Pneu monia George A Streeter Thomas W Farmer and Guy S Hayes[3] investigated the presence of cold ag glutinins in 122 serums from 50 patients with atypical

(3) B ll J h H pk H p 7 60 66 J ly 1944

pneumonia, arbitrarily choosing a positive cold agglutinin titer of 1 40 as the minimum significant dilution On this basis, abnormally high titers were found in 40 per cent of patients In 20 patients with positive cold agglutinins, the levels ranged from 1 40 to 1 640 In several cases in which the rise and fall in agglutinins during the course of infection were followed, serum titers reached maximum levels in one to three weeks after onset and fell to normal during the subsequent two to four weeks However time at which agglutinins develop and disappear is variable In one patient a titer of 1 40 was still present 81 days after onset of illness

*Control serums from 190 patients with various infec*tious diseases tested for cold agglutinins showed titers of 1 40 or higher in 3 7 per cent of the cases Titer was 1 40 in four and 1 80 in two one showed a rise to 1 640 with subsequent fall during the course of type XII pneumococcic pneumonia The controls included two groups patients with respiratory diseases which might possibly be considered in the differential diagnosis of atypical pneumonia and patients with other illnesses not related to atypical pneumonia Among 104 with respiratory illnesses 2 (1 9 per cent) developed significant cold agglutinins one had beta hemolytic streptococci in the throat and the other had pneumococcic pneumonia *Among 86 patients with measles scarlet fever* mumps syphilis etc, 5 (5 8 per cent) had high cold agglutinin titers 4 of the 5 had syphilis

The authors hold that since significant titers of cold agglutinins develop in only half of the patients with atypical pneumonia this test has confirmatory value in some cases of primary atypical pneumonia but no definite diagnostic value in the individual case

Rib Fractures in Atypical Pneumonia Rolfe M Harvey[4] (M C A U S) makes the first report of this phenomenon which was observed in 19 of 500 consecutive cases of atypical pneumonia at a station hospital during the winter of 1942–43 Omitting one case in which there

(4) *Am J Roe tg n 1 5 487-493 Novembe 1944*

was a definite history of trauma incidence of rib fractures in the series was 3 6 per cent Figure 35 shows the site of the 34 fractures which occurred in these 18 patients In nine cases the fractures were multiple and in all but four they were on the same side as the pneumonic process All fractures occurred in the anterior axillary or midaxillary line presumably caused by the

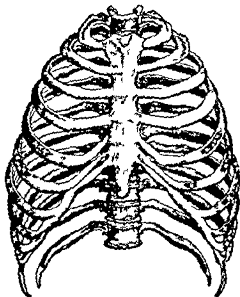


FIG 35 —Sket h f bo y th llu t t f t t E h h w t f f t

opposing forces of the serratus anterior and obliquus externus abdominis muscles (Fig 36) The occurrence of rib fractures was not related to severity of the pneumonia the severe dry cough was probably a factor in their production Excessive chest pain complained of by patients with atypical pneumonia should direct attention of roentgenologists to such complications since the fractures may be overlooked when study is centered on the inflammatory process In 10 of the 18 cases the frac

tures were not recognized until a routine review of the entire series was made in a search for them Many sup

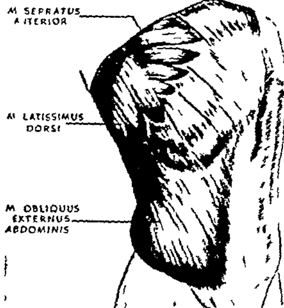


FIG 36 —I erd g t s f ser t a an erior lat ss d rsi a d obl quus ext rnus abdominis muscles. Compare with F gure 35

posed cases of pleurisy in atypical pneumonia may be explained by this complication

[Fracture of the rib may be caused by coughing from other conditions also and occasionally there may be dislocation of a costal cartilage The latter is a cause of severe pain the only physical sign is tenderness at the site of the trauma —Ed.]

Treatment of Pneumococcic Pneumonia with Penicillin Manson Meads, H William Harris and Maxwell Finland (Harvard Univ) report results of treatment in 54 cases, in 37 of which penicillin alone was given (group I) and in 17 of which sulfonamides were administered before penicillin therapy was started (group II) Since constant intravenous injections of penicillin caused difficulties, intermittent intramuscular injections were

(5) New Eng' nd J Med 23 747 755 J no 79 1945

used generally The average total dose and duration of treatment in each of the various groups of ca es in which

TABLE 1—DOSAGE OF PENICILLIN AND DURATION OF TREATMENT IN CASES WITH RECOVERY

Type of Case	Av Total Dos Units	Av Duration of Treatment H
Group I	411 000	86
Group II	[illegible]8 000	16
Severity		
Grade 2	317 000	66
Grade 3	47[illegible] 000	107
Grade 4	[illegible] 5 000	148
All cases	50[illegible] 000	107

recovery occurred are shown in Table 1 Supportive and symptomatic therapy including proper hydration and use of oxygen digitalis sedation and stimulants was used as indicated The effect on the clinical course as judged by duration of fever and acute symptoms such

TABLE 2—DURATION OF FEVER AND ACUTE SYMPTOMS AFTER FIRST DOSE OF PENICILLIN IN CASES WITH RECOVERY

	Group I	Group II	All Cases
Duration of fever (100 F or higher)			
1 hr or less	9	4	13
13–24 hr	5	2	[illegible]
25–36 hr	7	1	8
37–48 hr	3	1	4
More than 48 hr	6†	6	1[illegible]
Duration of acute symptoms			
1 hr or less	7	0	
13–24 hr	14	5	19
25–36 hr	5	1	6
37–48 hr	1		4
More than 48 hr	3	5	8

Tw f th p t t w still nt ly ill but had n fe wh pen ill w tart d
†O f th p t t d d t be m f b le n til fte p illin w t pped a d ulf n m d wa g

as delirium prostration and dyspnea after penicillin was started is shown in Table 2

In 18 of the bacteremic cases blood cultures were taken 24 hours after beginning of penicillin therapy In

only four were the cultures still positive, however they became negative 6–20 hours later In none of the cases of group I or II did a purulent complication develop after penicillin therapy was started There were only two complications that could be attributed to the penicillin sciatic neuritis in one case probably due to local

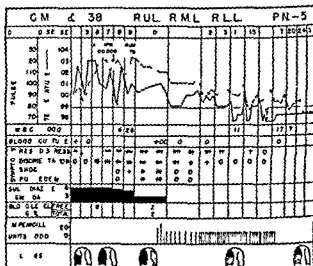


Fig 37 —Severe pneumonia with involvement of entire right lung on admission Patient had been treated with sulfadiazine for about six days at home and had adequate blood level of drug when admitted. Steady drop in temperature after penicillin was started clinical improvement followed

nerve injury caused by the intramuscular injection, and a *morbilliform rash* in one case *There were 10 deaths*, 7 occurring in moribund patients a few hours after treatment was begun and 3 in patients with severe complicating conditions

Tests for sensitivity to penicillin were carried out on 36 strains of pneumococci The minimal inhibiting concentration was 0 016 units or less per cc for 27 of the strains and 0 032 units for the remaining strains Blood levels corresponding to the minimal inhibiting concentrations or higher were rarely maintained for more than two hours after an intramuscular injection of 15 000

units There was no apparent correlation between sensitivity of the strains and clinical response

Penicillin is the treatment of choice and should be used from the start in patients who are extremely ill and in a shock like state in patients with cardiac renal or hepatic damage especially when there is azotemia or edema since with penicillin it is not necessary to give alkalis and large amounts of fluids which may result in serious water retention in such cases in patients with severe leukopenia and in those known to be sensitive to sulfonamides A change from sulfonamides to penicillin is indicated in patients who have adequate blood levels but have not improved after 24 hours or longer particularly if there is spread of the pulmonary lesion persistent bacteremia or an increase in pneumococci in the sputum as seen in direct smears The change to penicillin is also indicated if leukopenia delirium tremens auricular fibrillation or pulmonary edema develops before the symptoms of pneumonia have cleared or if severe untoward reactions such as acute hemolytic anemia gross hematuria oliguria anuria nitrogen retention and even drug rash occur before the pulmonary infection has been controlled Crystalluria or microscopic hematuria need not be considered a cause for stopping sulfonamides but is an indication for alkalis and increased fluid intake Penicillin may be used locally when infected pleural fluid or other accessible foci of infection develop and oral sulfonamides may be continued in such cases

Penicillin Therapy in Pneumococcic Pneumonia Morris F Collen and Alvin L Sellers[6] report on 646 consecutive patients with pneumococcic pneumonia admitted to the hospital between May 1944 and February 1945 Most patients received 5 Gm sodium sulfadiazine intravenously in 500 cc of $^1_6$ molar sodium lactate solution and 5 Gm sulfadiazine orally as an initial dose followed by 4 Gm sulfadiazine orally every six hours as the maintenance dose Adjuvant therapy in

[6] Permanente Found Med Bull 3 49 55 April 1945

the form of fluids expectorant cough mixtures, oxygen inhalation and alkali were used routinely In addition 126 patients (19 5 per cent) were treated with penicillin for the following indications (1) high pneumococci counts in the sputum, with evident or impending edema or shock severe toxic delirium leukocyte count below 6 000 or other signs of severe infection or toxicity, (2) failure to respond to adequate dosage of sulfadiazine and (3) pneumococcic type III pneumonia in patients over 40 Penicillin therapy alone was given to patients with (1) previous history of sulfonamide sensitivity or the development of sensitivity to sulfadiazine before the pneumonic process has cleared, and (2) cardiac failure renal insufficiency severe dehydration or acidosis In most patients penicillin was administered intramuscularly in doses of 25 000 units every three hours To prolong the effect of penicillin by delaying the rate of absorption ice bags were applied to the site before and after injection Frequently penicillin was given in doses of 100 000–200 000 units daily by continuous intravenous drip Penicillin therapy was continued until the patient was afebrile for 48 hours

The mortality in the 646 patients was 1 1 per cent In a previous group of 748 patients with pneumococcic pneumonia comparable except that penicillin was not used and type specific serum was used in *20 9* per cent the mortality was 6 2 per cent Penicillin proved very effective in pneumococcic type III pneumonia The additional use of penicillin did not alter materially the incidence of complications Toxic reactions to the drug were rare In 4 per cent of patients receiving penicillin intravenously local thrombophlebitis developed two patients had generalized urticaria and a febrile reaction *developed in one Causes of failure of* combined sulfadiazine and penicillin therapy were (1) admission to the hospital in a moribund state (2) inadequate doses of either drug or both due to (*a*) inadvisability of administration because of drug sensitivity (*b*) insufficient amount of drug given or (*c*) development

of the organism to the blood concentration of the drug (3) presence of severe associated diseases which could have been fatal in themselves

Absorption of Aerosol Penicillin via the Lungs Administration of penicillin may on occasion present difficulties Pain from repeated or long continued injections extreme youth of patients rapidity of excretion and the destructive effect of gastric juice all introduce therapeutic handicaps Some of these difficulties may be circumvented by absorption of penicillin via the respiratory tract particularly the lungs F A Knott and W H Clark[7] used true aerosols of penicillin dispersed by an electrically driven generator and found that at room temperature a penicillin aerosol remained fully active for at least 90 minutes Numerous tests carried out on themselves and four adult volunteers showed that a 15 minute exposure to aerosol penicillin resulted in a urine completely inhibiting the growth of a sensitive Staphylococcus aureus in a dilution of 9 parts of broth to 1 part of urine Exposure for 30 minutes resulted in inhibition in a dilution of 19 parts of broth to 1 part of urine After exposure for 15 30 minutes the inhibition range of the blood using a moderately sensitive beta hemolytic streptococcus fell between 1 in 2 and 1 in 3 dilutions of the blood The authors concluded that aerosol penicillin can be absorbed in therapeutic quantities by way of the respiratory tract direct from the room atmosphere without use of a mask and without any discomfort

The possible clinical applications of aerially distributed penicillin includes simultaneous treatment of several adults or children in a room or ward For individual patients especially small children the aerosol may be distributed by means of any simple tent technic Small aerosol generators can be activated from an oxygen cylinder The most obvious application seems to be in pneumonia bronchial infections and carrier condition particularly in the extremely young Moreover aerosol distribution of penicillin since it can produce complete

(7) La et 1 4f8 Ap 14 1945

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(7) Lancet 1 468 Ap 14 1945

bacteriostasis on surfaces 20 ft from the generator might be valuable in the operating theater when the risk of secondary infection is high or when difficult septic dressings are done

[It is to be anticipated that methods will be developed for administering penicillin by mouth overcoming the difficulty caused by destruction of the antibiotic by the gastric juice A number of studies in this direction have already been recorded —Ed]

Anemia and Hypoproteinemia Complicating Severe Protracted Pneumonia Treatment with Penicillin—Role of Specific Supportive Treatment S Howard Armstrong Jr Albert C England Jr, Cutting B Favour and I Herbert Scheinberg[8] (Harvard Univ) report the development of severe and progressive anemia and hypoproteinemia in two patients with extensive and protracted bacterial pneumonia treated with penicillin In Case 2 (man 85) the hypoproteinemia and anemia encountered at onset of the illness may well have been related to a deficient diet over a prolonged period To the disease itself could be attributed only a progressive drop in blood values already low The extent of involvement of pulmonary tissue by pneumonitis was not sufficient to lead to dangerous respiratory embarrassment so that once progression was checked by intensive therapy impaired oxygen capacity and diminished plasma colloid osmotic pressure did not contribute significantly to the respiratory picture In contrast the history and physical appearance in Case 1 gave no basis to suspect either hypoproteinemia or anemia antecedent to onset of illness *Moreover although penicillin and serum effected* apparent bacteriologic arrest on the tenth day of illness pulmonary involvement was so extensive that the patient was in desperate need of symptomatic treatment directed at morbid respiratory physiology

An increasing frequency of such cases is anticipated as powerful antibacterial drugs permit control of infection otherwise rapidly fatal The fact that in the present cases enormous amounts of whole blood and plasma together with nearly all known measures for maintenance

(8) J A M A 1 7 303 306 Feb 10 194

of optimal gas exchange in remaining functional lung tissue appeared necessary to maintain life for some time after apparent bacteriologic arrest of the infection suggests that in pneumonias of this severity development of anemia and hypoproteinemia should be anticipated by early use of whole blood and plasma together with adequate protein dietary intake

Progress of Resolution in Patients Treated with Sulfonamides Under chemotherapy delayed resolution is one of the commonest complications of lobar pneumonia In presulfonamide days the incidence of delayed resolution was 4 per cent it now lies between 25 and 30 per cent In the Glasgow report on pneumococcic pneumonia (1938–42) the association of certain factors with the incidence of delayed resolution was studied The most important factor was found to be age delayed resolution being twice as common among patients over 40 as among those under 40 Other pertinent factors were bacteremia duration of illness prior to hospitalization and infections caused by types II and III pneumococcus

Constance A C Ross[9] (Knightswood Hosp) studied other factors related to resolution namely the blood sedimentation rate and plasma protein level on admission Study of the former in 55 patients revealed that in cases of normal resolution the sedimentation rate although initially high returns to normal by the end of the third week whereas in delayed resolution it is still well above normal by the fiftieth day The height of rate on the twenty first day was of value in prognosticating the degree of delay in resolution Plasma protein estimations were made on 59 patients with pneumonia and on 23 healthy controls Sixty three per cent of patients with delayed resolution had total plasma proteins below 6 Gm (normal 6–8 Gm) while only 9 3 per cent of those with normal resolution and none of the controls had values below this figure The diminution was in the albumin fraction the globulin and fibrinogen showing no significant change Eighty five per cent of patients with

(9) Glasgow M J 96 February 1945

delayed resolution had albumin levels below 4 Gm (normal 4–5 5 Gm) In both normal and delayed resolution there was a gradual fall in total plasma protein values which was related to the length of time the patient had been ill prior to admission This suggests that pneumonia causes a fall in plasma proteins It is assumed that individuals who have low plasma proteins initially cannot respond adequately to the demand and delayed resolution results It is possible that the increase in cases of delayed resolution noted since introduction of sulfonamides is related as much to low plasma protein levels due to the prevailing dietetic insufficiency as to chemotherapy

[According to experimentation with rats conducted by Robinson and Siegel (*Journal of Infectious Diseases* 77 127 13 , September October 1944), resistance against induced pneumococcic lobar pneumonia is lowered by thiamine and possibly pyridoxine deficiency but not by other vitamin deficiencies. Inanition had no apparent influence on the resistance of the rats —Ed]

Plasma Volume and Extravascular Thiocyanate Space in Pneumococcic Pneumonia were studied by David D Rutstein K Jefferson Thomson Daniel M Tolmach William H Walker and Robert J Floody[1] (Albany Med College) Plasma volume measurements were made on 52 patients of whom 46 recovered and 6 died Measurements of the extravascular thiocyanate space were made on 26 of the 46 patients who recovered and on 5 of those who died The extravascular thiocyanate space is defined as that value obtained when the plasma volume as determined by the method of Gibson and Evans is subtracted from the total available fluid volume determined by the sodium thiocyanate method described by the authors

Results show that the mean plasma volume and the mean extravascular thiocyanate space increase significantly during pneumonia and decrease to levels below normal immediately after recovery The mean plasma volume in fatal cases of pneumonia is significantly lower than similar measurements in nonfatal cases This finding correlates with the clinical observation of peripheral

(1) J Cli I t gat 4 11 20 J ry 194

circulatory failure in these cases The venous hematocrit index red blood cell count and hemoglobin level and the determinations based on them (mean corpuscular volume mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) are unchanged during pneumonia The increase in plasma volume indicates that the total circulating solutes are diminished less than would appear from measurements of the concentration of such solutes Increase in plasma volume during the acute phase of pneumonia offers a possible explanation for the precipitation of congestive heart failure in cardiac patients with pneumonia This suggests that caution should be exercised in administration of fluids to such patients even if they had no previous attack of congestive cardiac failure The decrease in plasma volume and extravascular thiocyanate space immediately after recovery may prove of interest in a consideration of the circulatory readjustments occurring in convalescence

[As sugge ted by Meads and otle s (th s YEAR BOOK p 98) the increase in plasma volume f manifested by congestive heart fa lure is an indication for the u of pen cillin since th s does not nece sitate introducing adde l flu d an l alkal as is the ca e with sulfad a ine —Ed]

Postoperative Pulmonary Complications in a consecutive series of 2 000 operations with notes on management and treatment are reported by C Arkles (S A A M C) The incidence of pulmonary complications in the whole series was 2 3 per cent the incidence in abdominal cases was 9 per cent and in nonabdominal cases 0 2 per cent In preoperative prophylaxis and treatment special attention was paid to the general condition of the patient preoperative respiratory infection and improvement in vital capacity Except in acute cases when the operation could not be postponed respiratory infection received first attention A preoperative cough always becomes worse after abdominal operations restriction or elimination of smoking helps greatly Breathing exercises to improve vital capacity are an important aid in prophylaxis The patient s chest expansion was determined the poorer the expansion the poorer the postoperative

H p R p 93 79 86 1944

outlook regarding chest complications The more the breathing is abdominal the greater the need for breathing exercises to avoid the risk associated with laparotomy In a patient whose chest wall is so rigid that breathing exercises are of no avail indications for surgery must be carefully weighed against the risk involved

Postoperative prophylaxis and treatment consisted in avoiding use of the many tailed bandages leaving the patient recumbent except when the operation demanded the propped up position encouraging movement in bed after recovery from the anesthetic and starting breathing exercises Treatment of atelectasis and bronchitis consisted of postural manipulation and induced coughing Bronchopneumonia was treated by standard methods Fifty per cent of the patients with atelectasis and bronchitis became afebrile and convalescent in 48 hours and 75 per cent in 72 hours One patient with bronchopneumonia died

Experience in this series showed that the anesthetic agent played a negligible part in causing postoperative pulmonary complications The role of the surgeon is important the more gentle the handling of the patient the less the incidence of chest complications De Takats has shown that abdominal manipulation produces reflex bronchial spasm Since both pulmonary subventilation and bronchial spasm or reduction in vital capacity, may cause postoperative pulmonary complications roughness on the part of the surgeon may be considered an important contributory factor

Staphylococcic Pulmonary Abscess Due to Trauma of Skin Jacob Schwartz (Beth El Hosp) reports a case

Man 50 was hospitalized Sept 18 194[illegible] for an illness which began on September 3 with chills and fever pain in the chest and a hacking cough. Two afebrile remissions had occurred followed by return of chills and fever On examination he appeared toxic temperature was 104 F pulse rate 106 and respiratory rate 24 Examination of the right chest disclosed dulness diminished breath sounds scattered râles and some limitation of motion The urine showed 4 plus albumin with h [illegible] nd gran

(3) J Mt S [illegible] H p 1 [illegible] 46 M y J

ular ca ts and 1 8 per cent ugar A culture of the sputum revealed mixed organ ms with Staphylo occus aureus predominating Roentgen examination of the chest on September 20 showed diffu e proliferative infiltrat on of both pulmonic fields interpreted as bronchopneumonia On O tober 4 there was a small amount of fluid at the left base which pers ted for two week then disappeared but the infiltrat on was st ll seen Repeated bloo l counts and sternal pun ture showed pers tent and progressive fall in total leukocyte with extreme shift to the left total absence of eosinophils marked lymphopenia toxic granules and severe secondary anemia

On September 28 blood culture was po it ve for hemolyti Staphylococcus aureus It was then revealed that about seven weeks before onset of the present illness an abrasion on the left arm had become infected and an abs ess had formed which after dis harging for two weeks completely healed On October 6 the patient was placed on penicillin therapy the culture was sterile on O tober 12 but was aga n positive on October 25 The temperature from the day of adm ssion unt l October 9 ranged from 100 to 104 F and was not influence l by either sulfonamide or pen cill n therapy Impr em nt tarte l on October 8 but the physical findings in the chest rema ned unchanged He was discharged on November 11 but was rea lm tted December 4 with a history of pain in the chest and fever of four days duration Phys cal find ngs in the chest were about the same as before There were septic temperature secondary anemia and leukocytosis After several days signs and symptoms of absce s formation at the level of the right s th intercostal space posteriorly became apparent X ray examination confirmed the diagnos s The abscess empt ed and refilled s veral times Postu al drainage sulfonam des and support ve the apy were used but surgi al drainage eventually became necessary He was discharged May 0 1944 in good condition

Trauma to the skin appears to have been a definite factor in the etiology in this case From a knowledge of similar fatal cases seen at autopsy the pathogenesis was reconstructed as follows The right axillary glands remained enlarged long after the skin abscess healed and the infection extended to the lungs either by multiple embolization of the lungs via the subclavian vein or by seeding of the lung with bacteria via the subclavian lymphatic trunk which empties into the subclavian vein Most small abscesses coalesce to form larger pulmonary abscesses Entrance to the systemic circulation by the causative organisms is effected by the pulmonary thrombophlebitis Probably the diagnosis of bronchopneu

monia made on admission was incorrect and the findings were those of miliary embolization of the lungs with a variable amount of reactive pneumonitis, it is likely that the apparent resorption of the exudate noted on serial x rays was due to partial disappearance of the pneumonitis

[The first stage of lung abscess is bronchopneumonia regardless of the route of infection The distinction from simple bronchopneumonia is due to the invading organisms and when these produce suppuration and necrosis abscess results —Ed]

Lung Abscess Caused by Bacteroides Necrophorus William P Callahan Jr Parker R Beamer and Anibal Roberto Valle[4] (Washington Univ) report a case with autopsy findings Because of the frequency of infections with Bacteroides necrophorus in cattle, swine and sheep the importance of the disease in man as an occupational hazard cannot be overlooked Instances of infection in veterinarians have been reported but in all cases the disease remained localized in the skin Although the usual primary focus is in the skin, lesions in the nasopharynx and larynx support the assumption that air borne or droplet infection may occur Human infection with Bacteroides necrophorus are probably much more common than previously supposed Routine anaerobic cultures and careful anaerobic studies in all cases of infections of obscure etiology may show this type of infection

Man 41 bought wool and fur and came in contact with the green hides of cattle and sheep which were believed to be the source of the air borne infection The absence of lesions on the body surface plus a history of sore throat and the finding of a purulent exudate on the inflamed tonsils suggested that the pharynx was the portal of entry of the organism into the body The abscess in the lower lobe of the right lung was probably caused by aspiration of the infected material The disease process was confined to the respiratory tract and there was an attempt on the part of the host to heal the infection by formation of a dense wall of fibrous tissue around the abscess cavity Rupture of the abscess occurred and there was spread of the infection to all other lobes of the lung A gram negative pleomorphic rod with filamentous and coccobacillary forms was isolated from the pulmonary lesions at autopsy The organism was an obligate

(4) J Th a Surg 14 31 ‘47 J n 1945

anaerobe which produced a small zone of hemolysis and acid and gas on dextrose maltose and sucrose serum agar Pathogenicity for rabbits guinea pigs and mice could be demonstrated Serum obtained from a rabbit hyp rimmunized with a known strain of Bacterium necrophorum agglutinated the recovered organism in dilutions of 1 3 0 and the specific antigen in dilutions of 1 640 On this evidence the organism was classified as Bacteroides necrophorus

Analysis of Massachusetts General Hospital Cases of Lung Abscess from 1938 through 1942 is presented by Richard H Sweet The report includes 120 cases Healing occurred in 71 (59 2 per cent) being spontaneous or nonoperative in 28 and resulting from operation in 43 Twenty two patients died (18 3 per cent) 11 without operation and 11 following operation The remaining 27 survived but were not cured 6 of these were not operated on and 21 were treated by drainage but not cured

Operation was performed on 75 patients either primary lobectomy or drainage with or without secondary lobectomy or pneumonectomy Primary lobectomy was performed in 15 The most frequent indication for operation was chronicity No patient whose abscess had existed for one year or over recovered without surgery Serious hemorrhage was the indication in two cases and location (right upper lobe) or extent of the disease in two an erroneous diagnosis of carcinoma led to lobectomy in one case Of the 10 patients on whom the tourniquet technic was used 2 died of sepsis Of the eight survivors empyema developed in six Of the five patients who had individual ligation and separate bronchial closure silk sutures being used throughout four made uncomplicated recoveries and one developed empyema the latter was the only patient not given sulfonamides In all cases of empyema following both technics recovery was complete All patients in this group remain cured The remaining 60 patients were treated by drainage of the abscess Results were disappointing despite the fact that most patients were operated on soon after admission Nineteen patients were cured 9 died and 32 are classi

fied as alive with the disease The last group includes those with a persistent cavity or bronchocutaneous fistula Eleven of these patients were cured subsequently by secondary lobectomy or pneumonectomy Primary healing occurred in two, the others had a complicating empyema which ultimately healed The criteria of cure were freedom from cough and expectoration disappearance of abnormal physical signs and x ray evidence of complete healing The postoperative mortality of the drainage operation in the 60 cases was 1 6 per cent as all deaths but one were due to progression of the disease

Of the 45 patients not operated on, 28 recovered spontaneously 11 died and 6 remained alive with disease after having refused operation Of those who died overwhelming infection was the cause of death in six brain abscess in four and complicating ulcerative colitis in one Operation was not advised in these patients as they were hopelessly ill In most of the patients who recovered spontaneously the disease was of 3½ months duration or less The usual symptomatic treatment bed rest and postural drainage was employed In only five was adequate sulfonamide therapy used

The results as compared with those in previous series from this hospital demonstrate that there has been a definite increase in the total number of cures by all methods of treatment The present figure is 59 2 per cent as compared with 49 2 per cent for the last series and 34 8 for the one before that The present mortality rate is 18 3 per cent as compared with 33 9 for the last series The percentage of spontaneous cures remains approximately the same The operative mortality after the drainage procedure dropped from 7 4 in the last series to 1 6 per cent in the present one The percentage of cures by surgery has risen from 29 9 per cent in the previous report to 35 8 in the present series Use of sulfonamides had no material effect on results in the present series The improved results if not due to a diminution in the virulence of the infection in the average case, are most likely due to a greater knowledge of the

disease and a better understanding of the principles of treatment

Pleural and Pulmonary Suppuration Treated with Penicillin is reported by J E H Roberts Oswald S Tubbs and Michael Bates[6] Ten patients with hemothorax resulting from penetrating wounds were treated by the usual procedure of keeping the pleural space dry by aspiration and in addition by injection of penicillin solution at each aspiration the dose varying with the likelihood of contamination (15 000–60 000 units) The hemothorax became infected in one case by coliform bacteria which are penicillin resistant The authors believe that in infected clotted hemothorax because of the difficulty of getting the drug into the infected loculi rib resection and evacuation of clots followed by penicillin treatment to prevent progress of the pleural infection to the stage of frank pus is indicated

Twelve patients with acute empyema were treated with penicillin In 11 the pleural exudate was already frank pus when treatment was started so that the value of penicillin in the early invasive stage could be observed in only one patient Sterilization is usually obtained readily in patients with frank pus but aspiration and intrapleural injection of penicillin alone result in so much pleural thickening that operative treatment is required as soon as thick pus forms Evacuation of all fibrin and subsequent closure of the wound may prove satisfactory in some cases but best results are obtained by drainage Intrapleural injection of penicillin will be most important in cases diagnosed at an early stage when the fluid is still thin and localization has not occurred This applies particularly to cases of streptococcic origin with the pneumonic process remaining active especially in children and the aged

Seven patients with secondarily infected tuberculous empyema were treated with penicillin Although the results were not dramatic the authors believe penicillin therapy is likely to be beneficial in this type of case ex

(6) La 1 1 39 4 J 13 194

cept when a penicillin resistant bacterium is implicated

Three patients with coagulase positive staphylococcic suppuration occurring in a deep part of a thoracoplasty wound were treated by aspiration and injection of penicillin In two the sutured part of the wound was not infected and the infected space was ultimately sterilized In the third infection spread from the superficial part of the wound to the underlying space which became secondarily infected by Pseudomonas pyocyanea and drainage became necessary

Sixteen patients with pulmonary suppuration were treated by systemic administration of penicillin With one exception all had been treated previously with sulfonamides without improvement The response of diffuse suppuration due to nonhemolytic micro aerophilic streptococci was good The lesion in the lung improved in all seven patients but extension to the pleural cavity was not prevented in two and two had metastatic spread to the brain Of six patients with suppuration due to a mixed anaerobic flora improvement was obtained in only one which was surprising in view of the rapid disappearance of such bacteria from two empyema cavities treated locally A single patient with localized pulmonary abscess due to Staphylococcus aureus and *Streptococcus haemolyticus* responded well Two patients with thoracic actinomycosis—both with pulmonary infection and extensive chest wall involvement—were treated with penicillin One showed dramatic improvement and is now well the other died of Pseudomonas pyocyanea pyemia originating from the infused vein In view of the extremely high mortality in actinomycosis of the chest penicillin should receive a prolonged trial in these cases

[In considering the use of penicillin in these conditions the article by Blades and others (this YEAR BOOK p 184) should also be consulted.—Ed.]

Masson Body' in Rheumatic Pneumonia Masson Riopelle and Martin in 1937 described an inflammatory reaction in the lungs of 13 patients with rheumatic pneumonia consisting of a peculiar type of cellular granulation tissue in the form of buds which filled ' ar

ducts and spaces They concluded that rheumatic pulmonary involvement was a specific process In 1944 Neuburger, Geever and Rutledge reported eight cases including both active and quiescent rheumatic fever in which they found similar granulomatous nodules which they termed Masson bodies Since such nodules were not found in 60 control cases of acute pneumonia passive congestion of the lungs with and without pneumonia and chronic organizing pneumonia they too concluded that these nodules are specific for the rheumatic lung and are equivalent to the Aschoff body in the heart

Peter A Herbut and Willis E Manges[7] (Jefferson Med College Hosp) studied microscopic sections of the lungs in 505 cases Among 150 cases of rheumatic heart disease Masson bodies were found in 4 per cent The nodules could be divided into early and late The early lesions which were characterized by a patchy distribution seemed to arise either in the septums proper or within the alveolar ducts or spaces the former being much less frequent Each consisted of a round or fusiform unilateral or bilateral bulging of the septum caused at first by fibrinoid necrosis of the wall and later by a gradual replacement with loose fibrillary connective tissue and a mixture of various types of inflammatory cells As the process progressed the nodules became more circumscribed but still retained their septal connections The distribution of the nodules in the late stage was also patchy In all sections in which Masson bodies were found however there were also a few irregular plugs of organizing or organized exudate These were essentially similar in structure and age to the Masson bodies and differed only in their external configuration Most of the granulomas seemed to be attached to the ductal and septal walls by narrow or broad pedicles and sometimes they appeared to be a direct expansion of the septum or the alveolar duct wall itself They were all sharply circumscribed and round oval or fusiform Often there was an external covering of a single row of flat or cu

(7) Am J Path 1 741 751 J l 194



FIG 38 (top) —From a of leumati f v r M n l dy of fib o s type attach d to s ptum t n p t s compo l of d s fib o s t nd covered w th single l y r f flat c ll H m t xyl n eos n educ d from × 00

FIG 39 (b ttom) —From ca f t on h ectas Se en Ma n bodi s of fibrillary type H m to yli e n red c d from × 0

boidal cells These granulomas could be divided into four types (1) fibrillary consisting of fibrin mixed with edematous fibroblasts and arranged concentrically (2) fibrous consisting entirely of dense fibrous

38) (3) granulomatous consisting of spindle cells large round and oblong cells phagocytes and small round cells (4) mixed forms of the other types Usually all types were encountered in the same patient

Sections of lung in the remainder of the 505 cases showed similar Masson bodies distributed as follows in 30 cases of organizing pneumonia 46 per cent in 25 cases of pulmonary abscess 20 per cent in 160 cases



Fig 40 —F m f b n l t M n b l f fib typ ((h d by th b d p d l mp d f d n fibro t nd h n mpl te e t l g f fi t ll H m t xyl eo d d f m × 30

of bronchiectasis (Figs 39 and 40) 16 per cent in 85 ca es of pulmonary tuberculosis 8 per cent in 40 cases of chronic interstitial pneumonitis 2 per cent and in 3 cases of periarteritis nodosa 1 case Bodies were not found in any of the 12 ca es of asthma

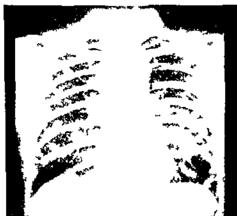
Because of the finding of nearby plugs of organized exudate in all the cases in which Masson bodies were found the authors believe that most of these bodies are organized intra alveolar and intraductal exudate and since they are found in a wide variety of pulmonary disorders are not specific for *rheumatic pneumonia*

Diagnosis and Treatment of Chronic Coccidioidomycosis are discussed by Edward J Denenholz and Garnett Cheney[8] (M C A U S) on the basis of 44 cases In 14 of these there was active coccidioidal infection This was of primary benign type in 10 and of progressive disseminated type in 4 In the other 30 cases coccidioidomycosis was suspected because of positive reactions to coccidioidin but was not confirmed The time from onset of disease to entry into the hospital in the 14 cases ranged from 4 weeks to 14 months and averaged 19 weeks In 8 of the 14 cases the admission diagnosis was erroneous

Denenholz and Cheney conclude that there are no pathognomonic symptoms or signs of chronic coccidioidomycosis, because clinical manifestations are varied and bizarre A history of exposure in an endemic area and evidence of pulmonary disorder should arouse suspicion Cough is present but not prominent expectoration is absent during the minimal or residual stage and pain in the chest is boring dull and worse at night A valuable diagnostic point is disparity between the strong roentgen evidence and the often completely lacking or minimal constitutional signs in patients with cavitation In disseminated coccidioidomycosis cutaneous lesions localized abscesses or prolonged fever may call attention to the disease The cutaneous test with coccidioidin is of great diagnostic value but a positive reaction has the same significance as a positive reaction to tuberculin and does not necessarily imply that the present illness is coccidioidomycosis A positive cutaneous reaction is however, of special value when a negative reaction has previously occurred A negative reaction generally precludes the possibility of coccidioidal infection Definite proof of the disease is obtained when the organism is grown on culture and on subsequent inoculation into a guinea pig or mouse produces characteristic spherules in the tissues

(8) Arch I t Med 74 311 330 No ember 1944

A positive sputum may be helpful when the serologic reactions are negative A diagnosis of disseminated coccidioidomycosis should rarely be made in absence of spe





F 41 (t p) —M 31 w th d m t d d d my s C t t t d d J g t th m th l t t w p t h w w k ss f d p h t l gi t s p t w th d d h gh t t t t gr i lly b m g t Film m (h ft t h w t d g f p m d t m

Fig 4 (b tt) —S m L ft l g m t f p l ul gl d ght p p ll m t l f h d

cific antibodies in high dilutions even if other data are suggestive However in primary benign infection negative serologic reactions do not rule out the disease

There is no roentgen evidence pathognomonic of coccidioidal pulmonary infection. A characteristic but not pathognomonic sign of chronic coccidioidomycosis is presence of a solitary thin walled balloon like cavity with little or no surrounding reaction and with a tend



FIG 43 (top left) —M[illegible] a[illegible] 31 [illegible] sem[illegible] at d[illegible] [illegible] mycosis of [illegible] Cutan[illegible] coccid[illegible] [illegible] following [illegible] the [illegible] [illegible] by [illegible] film [illegible]

FIG 44 (top right) —Same [illegible] 10 months later [illegible] uniform density of lower half of right pulmonary field extending up to interlobar pleura

FIG 45 (bottom left) —Film of same [illegible] 8 months after [illegible] tion of tenth [illegible] with [illegible] tion of [illegible] [illegible] destroyed Patient [illegible] [illegible] deceased [illegible]

FIG 46 (bottom right) —[illegible] film at same time

ency to persist The apparent resistance to either exogenous superinfection or endogenous reinfection of patients with pulmonary cavities is striking The most common pulmonary roentgen evidences of disseminated coccidioidomycosis are marked progressive pneumonic consolidation miliary dissemination and mediastinal adenopathy (Figs 41 and 42) Figures 43 46 show destructive lesions of thoracic vertebrae in a patient with disseminated infection Differentiation of coccidioidomycosis from tuberculosis in individual bone lesions is rarely possible

Treatment of coccidioidomycosis is mainly rest in bed to aid focalization Immobilization of the lung by a lead shot bag on the chest in a few cases in this series appeared to be of some benefit in helping to close thin walled cavities Use of immunotransfusions or of penicillin in disseminated coccidioidomycosis is worth a trial

[According to Lee (*California and Western Medicine* 61 13 1 4 September 1944) study of th s d sea e in the Western Flying Training Command showed that about "0 per cent of patients with diagnosed ca es will show sk n les ons about 1 per cent will develop d ssemination and four fifths of these will die —E1]

Healed or Arrested Pulmonary Coccidioidomycosis Correlation of Coccidioidin Skin Tests with Autopsy Findings E M Butt and A M Hoffman[9] (Univ of Southern California) performed coccidioidin skin tests on 1 165 patients Of these 302 (25 9 per cent) were positive Three major areas were represented San Joaquin Valley Arizona and Texas

Thirty six patients on whom skin tests had been performed and who died of various causes were examined by autopsy and postmortem roentgenograms of the lungs Twenty five had been negative reactors to coccidioidin With the exception of four all negative reactors showed calcified lesions of the lungs considered to be healed tuberculous foci All but three of the negative reactors had apical pleural scars The age limits of the negative reactors were 38–82 with most of them over 60 Animal inoculations and cultures made with material from these patients were negative for Mycobacterium tuberculosis

9 J P th 21 48 50 M y 194

indicating that calcified lesions in the higher age brackets are sterile regardless of their cause Spherules suggestive of Coccidioides immitis, but no endospores, were found in the calcified lesions of one of the negative reactors Material from two of the negative reactors, both dying of coccidioidal granuloma was positive for Coccidioides immitis on culture and animal inoculation These cases confirm the well known fact that patients with progressive coccidioidal granuloma may not react to coccidioidin In each of the two cases primary foci in the lungs and peribronchial lymph nodes of longer duration than the advancing pulmonary lesions were found

In all 11 positive reactors the calcified lesions of coccidioidomycosis were undistinguishable from similar lesions of tuberculosis except that apical scars were not a part of the healed or arrested pulmonary phases of coccidioides infection The primary disease resolves into one or more encapsulated fibrotic areas in various parts of the lung with associated single or multiple similar lesions in the peribronchial and tracheobronchial lymph nodes These lesions were so small in some cases as not to be revealed on roentgenograms taken during life The histologic pattern was essentially that of tuberculosis except for the presence of spherules The centers were caseous and contained small calcified particles and faint outlines of necrotic lung tissue Each lesion was surrounded by a dense hyalinized fibrous tissue capsule external to which there were collections of lymphocytes In older lesions the caseous material may be replaced by fibrous tissue Located in the capsules and caseous material were spherules of Coccidioides immitis and fewer large spherules containing endospores Many of the organisms were shrunken, distorted or ruptured Varying amounts of calcification were noted in some of the spherules Spherules were present in the healed lesions of eight of the positive reactors However endosporulation was noted in only 5 of the 8 or in 45 4 per cent of the 11 positive reactors

No clear clinical histories suggestive of coccidioido

mycosis could be obtained from the positive reactors This suggests that subclinical infections are more common than the acute clinical phase No cross antigenic relationship could be demonstrated between tuberculin and coccidioidin in this series Skin antigens of other fungi prepared in a manner similar to that for coccidioidin produced no skin reactions in patients reacting positively to coccidioidin A patient with cutaneous blastomycosis reacted negatively to coccidioidin in several dilutions With regard to its clinical significance the coccidioidin test is to be evaluated in the same manner as the tuberculin test

[Aronson Saylor and Parr (*Archives of Pathology* 34 31 7? July 194?) called attention to the calcification of pulmonary lesions due to this disease Cheney and Denenholz (*Military Surgeon* 96 148 156 February 1945) observe that some persons who previously reacted to coccid o din lose their sensitivity partially or completely within 6–1 months. These were nonclinical cases —Ed.]

Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin Carroll E Palmer[1] presents data based on records of tuberculin and histoplasmin tests and roentgenograms of 3 105 student nurses including 371 in Minneapolis and St Paul 859 in Kansas City Mo and Kansas City Kan 538 in Detroit and 7?7 in Philadelphia

Of the nurses studied 711 (22 9 per cent) had positive and 61 (2 per cent) doubtful reactions to histoplasmin Very great differences were found however in the percentage of nurses reacting to histoplasmin in the several cities in Minneapolis and St Paul 6 3 per cent gave definite or doubtful reactions in Philadelphia 12 6 in Detroit 14 4 in Kansas City Kan 54 and in Kansas City Mo 65 8 per cent Geographical migration tends to blur the marked regional differences

Of the 3 105 nurses 294 had pulmonary calcification About one fifth of these had positive tuberculin reactions Of the remaining four fifths who had negative tuberculin reactions 206 had positive or doubtful histoplasmin reactions Only 25 had negative reactions to

(1) P b H lth R p 60 513 5 0 M v 11 194

both tuberculin and histoplasmin Considering these findings altogether it is evident that a high proportion (91 5 per cent) of the group with pulmonary calcification reacted to tuberculin or histoplasmin or both and that many more reacted to histoplasmin than to tuberculin The association between calcification and tuberculin reaction is quite different from that between calcification and histoplasmin reaction Of nurses reacting only to tuberculin 10 4 per cent showed pulmonary calcification while of those reacting only to histoplasmin, 31 1 per cent showed calcification The percentage was higher (34 1) among those reacting to both antigens than among those reacting to either antigen alone Among the nurses who were negative to both tuberculin and histoplasmin a low rate of pulmonary calcification (1 2 per cent) was found

Palmer concludes that mild probably subclinical infection with Histoplasma capsulatum (or an immunologically related organism) is widely prevalent in certain states and relatively uncommon in others that in general those states in which the frequency of reactions to histoplasmin is high are those in which pulmonary calcification is also high and that a very high proportion of the pulmonary calcifications observed in roentgenograms of tuberculin negative persons is due not to tuberculosis but probably to histoplasmosis

[The importance of this investigation is evident Studies are now being made in parts of the United States to ascertain whether the findings can be amplified and verified by bacteriologic and pathologic studies Parsons and Zarafonetis (this YEAR BOOK p 118) have reported a detailed study of the clinical and pathologic features of histoplasmosis in man —Ed]

TUBERCULOSIS

The discovery that certain drugs particularly those of the sulfone series have a definitely inhibitory effect on tuberculosis in guinea pigs has stimulated numerous studies on chemotherapy For example Melville and Stehle (*Canadian Journal of Research* Sect E 2 95 1 1 December, 1944) report the study of 79 compounds and Freedlander (*California and Western Medicine* 61 85, August 1944) records the testing of 90 of

benzophenone A number of substances are found to have a bacteriostatic effect of varying de ree However the clini al trials which have been conducted have in no instance produced in human beings effects which are nearly comparable to those noted in guinea p gs

More or less simultaneously extens ve work has been carried on with a number of antibiotic drugs Several strains of the fungus aspergillus have been found to yield filtrates which in hibit growth of the tubercle bac llus Streptomycin an antibiotic substance obtained by Waksman and h s co workers from one of the actinomycetes (Streptomyces griseus) possesses striking bac teriostatic and bactericidal effects against Mycobacterium tuber culosis Feldman and Hinshaw (*Proceedings of the Staff Meetings of the Mayo Clinic* 19 593 599 Dec 2, 1944) found strepto mycin to be well tolerated by guinea pigs and to exert a strik ing suppressing effect on tuberculosis in the e animals when in fected with human type of the bacillus the effects are compa rable to those of some of the sulfone derivatives Here again thorough evaluation of the therapeutic action in cl nical tubercu losis must await much longer study Thus far it does not appear that the effects in man are positive constant or definite There fore physicians should be conservative and cautious in consider ing the use of the drugs and should warn their patients against overoptimism created by fragmentary reports in th lay press It is certain that the discovery of some substances which may be specifically helpful in the treatment of tuberculosis is more to be ant cipated now than ever before Because of the nature of tuberculosis in man it is probable that any such substance will not operate as strikingly and definitely as for instance peni cillin does in pneumonia

Meanwhile incidence of tuberculosis continues to decline in the United States the annual death rate now being in the neighbor hood of 40 per 100 000 This compares with approximately 200 per 100 000 in 1900 The present campaign for control and eradi cation must be credited w th great accomplishment and it must be continued and intensified —Ed

Tuberculosis in the Armed Forces According to Es mond P Long and Edward A Lew (Washington D C) the armed forces of the United States have at tempted to exclude as far as possible all cases of active or potentially active tuberculosis by chest x ray exami nation prior to acceptance of men and women for mili tary service or call to active duty In consequence the incidence of tuberculosis as determined by annual hos pital admission rates has fallen to the lowest figures on record The rates for both Army and Navy are less than one tenth of the average rate in World War I Discovery and exclusion of cases of tuberculosis by x ray examina

(2) Am J P b H lth 35 469-4 9 M 194

both tuberculin and histoplasmin Considering these findings altogether, it is evident that a high proportion (91.5 per cent) of the group with pulmonary calcification reacted to tuberculin or histoplasmin or both and that many more reacted to histoplasmin than to tuberculin The association between calcification and tuberculin reaction is quite different from that between calcification and histoplasmin reaction Of nurses reacting only to tuberculin 10 4 per cent showed pulmonary calcification while of those reacting only to histoplasmin, 31 1 per cent showed calcification The percentage was higher (31 1) among those reacting to both antigens than among those reacting to either antigen alone Among the nurses who were negative to both tuberculin and histoplasmin a low rate of pulmonary calcification (1 2 per cent) was found

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pital longer than three months Of the 46 in the first group 27 died 19 of miliary disease or meningitis Only 10 of the 197 patients in the second group died The children aged 18 months or less had a much higher death rate than did the older ones Of the 206 children who lived 194 had primary and 12 reinfection tuberculosis Of the 213 children admitted with primary tuberculosis 72 2 per cent were classified on discharge as having the disease apparently arrested These children had a lower death rate than those otherwise classified on discharge The patients who remained in the hospital longer fared four times better after discharge than those in the shorter hospitalization group For this reason the authors plead that children with active tuberculosis with or without symptoms be provided with adequate hospital treatment

Primary Tuberculosis Effect of Unrestricted Activity on Prognosis Milton L Levine[4] (Cornell Univ) from 1926 to 1942 studied over 1 000 children from tuberculous homes during and after the first year of life During the study gross parenchymal lesions of tuberculosis de veloped in 90 children 58 of whom were under 1 year Onset of the primary complex occurred in early infancy in 27 of these who were classified as nonambulatory Of the 27 16 died of tuberculosis and 1 had a complication—tuberculosis of the hip Of 60 children who were defi nitely ambulatory during the period of parenchymal involvement 4 died of tuberculosis and only 2 had com plications—tuberculous cervical adenitis in one and mul tiple hematogenous lesions in the other Only three chil dren over 1 year were hospitalized when the pulmonary infiltration was visualized one died of tuberculosis and one had a complication—tuberculosis of the spine

Careful study of roentgenograms revealed that in the 60 ambulatory children average time from parenchymal infiltration to earliest signs of calcification of the primary focus was 7 7 months and average time to complete cal cification was 21 1 months Wallgren who advised rest in bed for children with active primary tuberculosis

(4) Am J D Child 68 385 389 Dec 1944

tion was not perfect and a certain number of active cases not detected at induction were discovered later These individuals and those in whom the disease develops are discharged from military service after a period of initial treatment The annual rate of discharge from both Army and Navy for tuberculosis is now approximately 0 5 per 1 000 men Both branches require chest x ray examination before discharge of men and women from service

Discovery and rejection of cases of tuberculosis in pre enlistment and pre induction examinations, detection of cases in the course of military service or in the examination required on discharge and the present system of reporting to state health authorities have made the tuberculosis programs of the armed forces an outstanding contribution to the national program of tuberculosis control

Fate of Very Young Children with Tuberculosis Gertrude F Mitchell (Detroit) and Henry Stuart Willis[3] (Northville Mich) present data from records of hospitalization discharge and follow up experience for 243 children under 3 years admitted to Wm H Maybury Sanatorium in 1922–38 These children were classified on the basis of x ray findings as having primary lesions or reinfection Those having enlargement of tracheobronchial lymph nodes with or without signs of disease in the lung and those having characteristic pulmonary shadows without demonstrable lymph node enlargement were listed as having primary tuberculosis Those with pulmonary disease and calcium deposits in pulmonary fields were listed as having reinfection (30 children) Of the 243 children 153 were white and 90 Negro The mortality rate among Negro children was twice that among white children The outlook in both races was distinctly worse with reinfection than with primary lesions Of the children with reinfection 18 or 60 per cent died in hospital

The children were divided arbitrarily into two groups (1) those in hospital three months and (2) those in hos

(3) Am Rev T berc 50 316 3 9 O t ber 1944

hospital group The group with the higher conversion had a high proportion of strongly positive reactions revealing conversion Most had no notable symptoms between the last negative and the first positive test The more rapid conversion in A hospitals was probably due to greater degree of exposure to patients with open cases of tuberculosis

Study of tuberculous morbidity in nurses who entered the survey before 1942 and whose chest x ray on entry was clear revealed 33 cases occurred in 452 nurses initially Mantoux negative and 43 in 2 120 nurses initially Mantoux positive Of the former only 19 (6 9 per cent) had detectable lesions probably representing a primary focus a primary complex was seen in 8 a pulmonary focus only in 8 and a hilar focus only in 3 The disease was uncomplicated in 6 more severe in 3 complicated by pleurisy only in 4 by lesions of dissemination in 2 and by pulmonary lesions probably of secondary infection in 4 Only two patients had a typical uncomplicated Ghon focus Excluding those with uncomplicated primary focus and taking the date of onset in those with primary focus followed by secondary lesions as that of the secondary lesion 17 of the 27 initially Mantoux negative and 19 of the 43 initially Mantoux positive cases arose during the first two years after entry The annual case rate among the Mantoux positive on entry was 7 4 per 1 000 among the Mantoux negative 18 8 per 1 000 When last heard of 2 of the 27 initially negative nurses had died of phthisis in 7 the lesions were still active in 4 quiescent None of the 43 initially positive died in 14 the disease was still active in 19 quiescent Acquired immunity is clearly partly responsible for the lower rate of tuberculosis in Mantoux positive nurses but other factors may play an important role such as previous elimination of susceptibles In addition repeated infections following primary infection may determine the lesions in some cases

The evidence of this survey and 20 other surveys shows that risk of development of tuberculosis following pri

states that the first trace of calcification is generally seen after 1-1½ year and calcification is complete in 2-3 years There is, therefore no evidence that rest in bed influences the course of the primary complex in any way or reduces incidence of complications, or that lack of rest in bed is in any way detrimental Apparently age of the child at the time of infection rather than the method of treatment is the important factor in mortality from tuberculosis in early childhood Rest in bed in primary infection as in any other febrile condition in childhood, should be limited to the period of fever

The study presented further evidence of the importance of intimate contact of the 58 infants in whom parenchymal pulmonary lesions developed before the age of 12 months 19 were exposed to their mothers and 28 to their fathers 52 6 of the former and only 21 4 per cent of the latter died of tuberculosis

[This and the preceding article reflect the difficulty met in trying to evaluate the effects of treatment in a disease as variable as tuberculosis The common assumption that primary tuberculosis is harmless is far from correct Most clinicians will take a serious view of tuberculosis in young children and by close supervision and regulation of the way of living will attempt to safeguard these patients against progressive disease —Ed]

Primary Tuberculous Infection in Nurses Manifestations and Prognosis Marc Daniels[5] (London) reports on data collected in one of the groups under observation in the Prophit Tuberculosis Survey From 1935 to 1943 3 764 student nurses were drawn from two groups of general hospitals A' hospitals which admitted all types of cases all having tuberculosis wards and B' hospitals which rarely admitted chronic cases, only one of the 6 having a tuberculosis ward Mantoux tests had been given and roentgenograms made shortly after the nurses had entered preliminary training Of the 3 764, 50 3 per cent were positive to OT 1 10,000 or 1 100 000, 30 5 per cent were positive only to 1 100 or 1 1 000 19 2 per cent were negative The rate of Mantoux conversion during the first year of training was 78 3 per cent in the 'A hospital group and 58 4 per cent in the 'B

(5) Lancet 2 16 1 0 A g 5 01 04 Aug 1 1944

seminated bronchiogenic) Such factors as the number and viability of bacilli causing the primary infection the environment the nature of the infecting source and acquired resistance (allergy economic conditions or repeated superinfection) will decide the form of postprimary tuberculosis if such manifestation develops

[The important and extensive studies of Terplan which have been reported by him during the last few years should be consulted by those interested in the pathogenesis and evolution of tuberculosis —Ed]

Latent Tuberculous Reinfection in Man A Saenz and G Canetti[7] (Montevideo) find that latent tuberculous reinfection is common in man probably occurs repeatedly in the same individual produces anatomic lesions with abortive tendencies leading mostly to final sterilization and has a definite effect on tuberculin sensitivity Latent reinfection also offers proof of the general resistance of mankind to tuberculosis for in four fifths of the persons so affected it remains clinically asymptomatic

On the basis of autopsies of persons over 45 who died of nontuberculous causes the authors believe that two thirds of their countrymen have nonapical or apical reinfection lesions with apical nodules occurring much more frequently Nonapical nodules are subpleural usually in the upper lobe and have the same anatomic features as the lesions of primary infection However there is almost constant absence of involvement of satellite lymph nodes The apical nodules especially those found in the apex resemble anatomically the so called slate colored pneumonia of Cruveilhier Seventy five per cent of persons with latent reinfection presented more than one nodule and 44 per cent more than two Similar statistical studies of other authors carried out on subjects of all ages reveal that latent reinfection does not occur under the age of 20 is extremely rare under 30 and shows an increased incidence thereafter at any age Since primary infection is most common under the age of 20 the authors consider it unreasonable to be

(7) S hw med W h 4 78 794 J ly 2 1944

mary infection in young adults is serious A controlled method of vaccination is needed In absence of vaccination it is recommended that patients with open tuberculosis should not be admitted to general wards, droplet and dust borne infection should be prevented, tuberculin negative nurses should not nurse in tuberculosis wards, nurses should be retested every three months Nurses known to have been recently infected should have routine monthly check up on weight temperature, respiratory infections etc, and chest x ray examination at three month intervals during the first year and at six month intervals during the next two years

Origin of Bronchiogenic Tuberculosis in the Adult Walter Pagel[6] states that late primary infection is prone within a short time to cause an Assmann focus i e, a postprimary caseous change preferably in the infraclavicular area of the upper lobe, which by its tendency to cavitation and spread via the bronchial system causes the common bronchiogenic tuberculosis of the adult While it is theoretically possible that these foci are due to a new exogenous reinfection their quick succession on primary infection and the interposition of small disseminated notably apical nodules (so called Simon foci) as shown by Malmros and Hedvall suggest that all these are manifestations of the same infection The findings of Malmros and Hedvall are in conformity with the morbid anatomic findings that a primary focus—old or fresh—precedes bronchiogenic tuberculosis in all cases, in adults as well as in children The theory is supported by the pictures of recrudescence of old especially calcifying, postprimary foci and the common occurrence of solitary Assmann foci in cases of disseminated tuberculosis which is blood borne In other words the postprimary changes are related to the primary focus they are due to hematogenous dissemination from it

Inborn resistance decides the severity of the infection in the individual it does not decide the type in which tuberculosis manifests itself (primary postprimary dis

(6) B M J 91 Dec 16 1944

fatigue Except in a small number of cases the sputum was negative for tubercle bacilli at the time of initial examination the concentrated method being used in most instances

Roentgen findings may be regarded as the most important single criterion for determination of the clinical significance of the minimal tuberculous lesion in this type of ambulatory patient The lesions were classified in four groups according to their predominant features In exudative lesions the density usually shows ill defined borders is soft in appearance round or irregular in shape and ranges from 1 to 3 cm in diameter The individual lesion may represent a single focus or be composed of several small confluent densities The underlying pathologic change is assumed to represent a pneumonic infiltration involving the parenchyma of the lung with or without caseation but not yet progressed to cavitation Two main forms of productive fibrotic lesions are seen discrete nodular densities usually multiple small and with well defined borders hard and round or irregular in shape or strandlike or linear densities sharply outlined and often irregular in shape and distribution Most patients present a combination of the two The pathologic changes are probably miliary or acinous nodular foci consisting of tuberculous granulation tissue fibrosis or both The stringy or linear densities represent fibrous tissue arranged in strandlike fashion Exudative productive lesions may be regarded as an intermediate group between the former two In fibrocalcific lesions the changes consist of sharply defined nodular densities with round or irregular borders They are usually multiple scattered and small rarely exceeding 1 cm and are usually interpreted as characteristic of calcium deposition The underlying morbid changes are assumed to be calcareous or cheesy calcareous foci usually in combination with varying degrees of fibrosis (advanced anatomic healing)

Of the total 47 per cent had lesions of the exudative or exudative productive type about 33 per cent had

lieve that the same bacilli which produced it also cause latent reinfection. The latter is therefore the result of continued exposure to exogenous bacilli.

Statistical reviews of tuberculin sensitivity in a large number of subjects at all ages have shown that in those who at one time reacted strongly, the allergic response is increased as age advances. The authors believe, therefore, that latent reinfection rekindles the attenuated sensitivity to tuberculin left by previous infections. The tuberculin allergy of an individual throughout life is a sum total of multiple, overlapping and different allergies —different because produced by different infections, at a different age and on different terrains modified by previous infections.

The most striking feature of lesions of latent reinfection is that they represent irrefutable proof of repeated tuberculous attacks successfully overcome and emphasize the preponderance of tuberculous infection over tuberculous disease. However, since 10–20 per cent of persons continuously exposed to tubercle bacilli do acquire pulmonary tuberculosis, tuberculosis control should combat all possibilities of tuberculous contamination, especially in the remaining fifth of individuals who are not able to sterilize their reinfection lesions completely and who may be candidates for tuberculous disease.

Minimal Tuberculous Lesions of the Lung: Their Clinical Significance. David Reisner and Jean Downes[8] (New York City) made a study of 469 patients, including 291 whites and 178 Negroes and Puerto Ricans. There were 200 males and 269 females. No patient was under 10—24 per cent were adolescents or young adults, 58 per cent were between 25 and 44, and 18 per cent were 45 or older. In most cases the pulmonary lesions were discovered on routine chest roentgenograms. In 76 per cent of the total there were no significant subjective symptoms at the time of initial diagnosis. About 10 per cent had had hemoptysis or blood streaked sputum, 13 per cent had lost weight, and 11 per cent complained of

(8) Am. Rev. Tuberc. 51: 393-41, May 1945.

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Of the total 47 per cent had lesions of the exudative or exudative productive type about 32 per cent had

lesions of the productive and fibrotic type, and 14–20 per cent had lesions of the fibrocalcific type Period of observation ranged from 2 to 10 years, 50 per cent of the patients were observed for 5 years Behavior of the lesions determined by means of serial roentgenographic studies during the follow up period was classified into four main types frankly progressive unstable, regressive with subsequent stabilization and stationary

Character of the lesion at initial diagnosis was found to be closely related to behavior of the lesion and risk of progressive disease Lesions of the exudative or exudative productive *type are characterized* by unstable behavior and a distinct tendency to progression Progression was observed in about 50 per cent of the white patients and in 61 per cent of the Negroes and Puerto Ricans Lesions classified as productive fibrotic or fibrocalcific showed a stationary character in most instance *Lesions of the fibrocalcific type* showed *the highest rate* of stability and only exceptionally were progressive The minimal lesion of exudative character presents a definite hazard Approximately half of the cases in this group presented evidence of active tuberculosis at the end of the observation period most of them having progressed to advanced stages of the disease *Only 3–5* per *cent of* the productive fibrotic and fibrocalcific lesions had a diagnosis of active disease at the end of the period of observation

For evaluation of the *results of treatment* in minimal tuberculosis it is of great importance to consider the character of the lesion at the time of initial diagnosis The exudative type of lesion is an indication for therapeutic intervention and supervision of the case over extended periods Patients with minimal lesions of chiefly fibrotic or fibrocalcific type usually may be allowed to carry on their normal mode of life unless there are signs suggestive of activity

[One of the most important responsibilitie of physicians is to appreciate the potential danger of small tuberculous lesion particularly in young people and to advise proper treatment for a sufficient length of *time* As yet there is no for

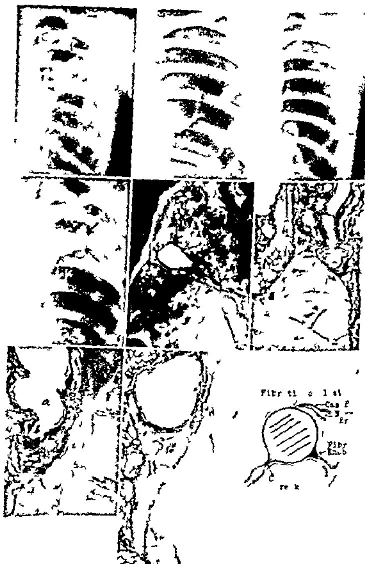
ing the period of rest treatment which in the case of the small soft pneumonic lesion usually requires at least a year before dependable arrest of the case can be expected.—Ed.]

Closure of Tuberculous Cavities John Loesch[9] (Oneonta, N. Y.) presents a detailed anatomic study of complete closure of cavities in five cases with six cavities. In four cases treatment was by pneumothorax and in one by bed rest. A sixth case in which the cavity had shrunk markedly during strict bed rest is included as a transitional case.

The mechanism was mostly one of shrinkage of the cavity with simultaneous contraction, approximation and final obliteration (1) of the cavity outlet, (2) the tuberculous bronchus at the point of transition into the normal portion by fibrotic tissue or (3) of both these areas when caseous material was retained in the diseased bronchial portion between them. Shrinkage of the cavity outlet occurred in Case 1. The cavity was of short duration and the draining bronchus was not involved by tuberculosis. Shrinkage was also found in the outlets of bronchi 2 and 3 in Case 2 (Figs 47-50). In outlet 2 its occlusion extended beyond the focus in the form of a triangular knob toward the intact bronchus. In outlet 3 the tributary bronchus showed diffuse caseous involvement. Outlet 1 and the adjacent bronchial portion were markedly contracted, containing a caseous streak in the lumen. The second type of closure was seen in Case 3 in which the inspissated caseous material, partially calcified, extended for some distance into the lumen of a large caseous bronchus filling it out completely. The same mechanism prevailed in Case 5, except that one bronchial lumen was filled in its entire length distal to the fibrotic tissue with epithelioid cell granulation tissue and the other with a fibrotic cord, the latter representing the healed phase of the former. The third type of closure was found in the two cavities of Case 4.

After closure at points 1, 2 and 3 the cavities shrank further and the content retained became inspissated and finally partially calcified. Shrinkage in the transitional

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case was due to a plug which occluded the outlet of the cavity favored by endobronchitis absence of peristalsis fibrotic peribronchitis and position of the diseased bronchus which branched at a right angle largely preventing passage of air from the main bronchus

In none of the inspissated foci in Cases 1 to 4 were tubercle bacilli found As oxygen and moisture are essential for the growth of the bacilli their almost total absence probably caused death of the bacilli An irregularly outlined radiolucent area which persists in the course of closure of a cavity may be interpreted as a residual cavity and may lead to unindicated therapy This interpretation was given during life in Cases 3 and 5 Postmortem examination proved the area to be an inspissated cavity

Nutrition in Tuberculosis As Evaluated by Blood Analysis Horace R Getz Irene S Westfall and Howard J Henderson[1] (Univ of Pennsylvania) present results of a nutritional study of 457 tuberculous and nontuberculous males attending on outpatient chest clinic of whom 41 per cent were Negroes The population studied resided in the underprivileged areas of Philadelphia where both tuberculosis and malnutrition are prevalent

Patients with active tuberculosis were deficient in ascorbic acid vitamin A hemoglobin and serum albumin in the order listed All nutritional deficiencies were more extensive and profound in tuberculous than in nontu

FIG 47 (t p w l ft) —C P ght upp l b t M y 0 1936 b f pn um th
F 48 (t p w t) —S m N 7 1936 d g p eum th
F G 49 (top w ght) —S me e, J 29 1933 d g p m th
F 50 (nt w l ft) —S m P t lly xp nd d lu g th d n f p ting f m t
FIG 51 (ce t w t) —S m se b t f ght uppe and m ddl l b th gh d f u fi b tw n l b bl t t d v al pl th k d l lghtly nd nt d pp t f u
F 5 (cent w ght) —S m S t th gh l g t d l f b h t m t g bl dly mn h m h p t t lay f p l f f
FIG 3 (b tt m w l ft) —S m S t n f dil t d b h ( ) d m ll b h (b) t p t f b h g ff f m f rm Sm ll h h w d ff eo b h t t m t bl dly t t l f psul f f u nd p d n t t l gth g t l tt (F g 4)
FIG 54 (b tt m w t) —S m
FIG 5 (bott m w ght) —S m D w g f l l ty d th I tt f l

(1) Am R T be 50 96 111 A gu t 1944

berculous subjects Patients with far advanced tuberculosis were especially deficient in ascorbic acid, serum albumin, hemoglobin vitamin A carotene and serum calcium in the order given Serum calcium was normal in minimal and moderately advanced tuberculosis Nontuberculous patients were deficient in ascorbic acid hemoglobin vitamin A and serum albumin but to a lesser degree Subjects with arrested tuberculosis had nutritional levels about the same as nontuberculous subjects There was more active tuberculosis, and less of it was in *the minimal stage in the oldest age group (40–49) than* in the younger age groups Age and hemoglobin level showed a negative correlation the hemoglobin level remained constant as the age advanced Tuberculous and nontuberculous subjects had normal plasma levels of carotene with abnormally low vitamin A levels, indicating that conversion of carotene was at fault Plasma ascorbic acid level showed a positive correlation with the erythrocyte sedimentation test when the maximum five minute drop was used but not when the total sedimentation in one hour was used The sedimentation rate showed a positive correlation with the serum albumin concentration This fact may give a new significance to the sedimentation test

Studies on Vitamin K in Tuberculosis E Tanner and F Suter (Davos) performed prothrombin determinations in 58 cases of pulmonary tuberculosis Prolonged prothrombin time was found in 16 per cent Prothrombin levels showed no correlation with the extent of the pulmonary lesion but seemed to depend on activity (intensity) of the disease Prothrombin time was prolonged in 18 per cent of patients with active pulmonary tuberculosis, against *10 per cent of those with chronic tuber*culosis Patients with organic or toxic gastro-intestinal disturbances showed a greater incidence of prolonged prothrombin time than did those without gastro intestinal disorders (27 per cent against 13 per cent)

In five patients with thoracoplasty two with nephrec

( ) S hwe z med W hn h 74 55 5 4 May 0

tomy and three with pneumolysis prothrombin time during the first five postoperative days showed prolongation when compared with preoperative values The patients with pneumolysis showed prolonged prothrombin time despite vitamin K therapy The lowered prothrombin level during the immediate postoperative period is assumed to result from action of operative trauma and protein destruction in the operative wound on the liver Prolonged prothrombin time may be the cause of gastric hemorrhages following thoracoplasty Three of six patients with hemoptysis showed prolonged prothrombin time but in none of these was the prothrombin level near the critical value of 20 per cent encountered in patients with massive spontaneous hemorrhages In all three patients hemoptysis ceased before vitamin K was given

The most important effect of vitamin K is the increase and normalization of the prothrombin level This effect is also operative in tuberculosis However since prolonga*tion of prothrombin time was not striking in this series* and since vitamin K fails to show a vasoconstricting effect the authors hold that its usefulness is limited to cases of extremely active tuberculosis or tuberculous gastro intestinal disturbances

Value of Work in Treatment of Tuberculosis Frederick Heaf[3] recalls that use of work as a therapeutic measure in treatment of tuberculosis began when Paterson at Frimley during 1910–16 instituted a rigid system of rest and graduated exercises controlled by careful recordings of the patient s temperature pulse rate and opsonic index Later at Papworth Varrier Jones visualizing the psychologic value of productive employment as a stimulus to work disregarded the scientific basis of Paterson s treatment and began to give patients industrial work which eventually attained an economic value and offered a means of livelihood under the ideal environment of a village settlement

Institution of a well graduated program of work and rest therapy with proper control and supervision lays

(3) J et 1 63 64 M 3 1945

the foundation on which a sound structure of regulated sanatorium routine can be built Work therapy not only strengthens character and reliability in the patient but demands frequent periodic examinations and tests by the physician to enable him to assess the capacity and adaptability of the patient to the work In assessing this capacity however the present practice of relying on temperature and pulse rate records, with an occasional sedimentation test is insufficient for the exact prediction of the ability of a tuberculous patient to undertake work requiring a known energy output Evidence of cavity closure or retrogression of radiographic shadows does not necessarily indicate fitness for work Many patients with open cavitations can be safely employed in occupations which would be dangerous to many with minimal lesions Controlled diversional therapy can be undertaken with beneficial results by many patients with active disease and occupational therapy can be safely prescribed for patients with extensive radiographic shadows provided their capacity for work is known Orr and Leitch have estimated with considerable accuracy the energy required in calorie hours to perform certain types of labor which should form a basis for future research A simple and practical method of finding the maximum amount of energy which each patient can safely produce is needed to make possible the prescription of an occupation which demands an energy output below that amount

At a village settlement or sanatorium living and working conditions approach nearer to the ideal for the tuberculous person than anywhere else For this reason, as many ex patients should be employed on the staff of a sanatorium as possible Others should be employed in sheltered industries either in special workshops or in modified employment in normal industry Only those who are fully capable should be allowed to enter open labor markets where efficiency speed and mass production methods produce strain and may cause irreparable damage

Bronchoscopic Observations in Tuberculous Tracheobronchitis Clinical and Pathologic Correlation Norman J Wilson[4] (Boston) states that tuberculous bronchitis is a frequent and serious complication of pulmonary tuberculosis occurring in 10–15 per cent of the patients admitted to sanitoriums The study of surgical pathology indicates that the earliest bronchial lesions are submucosal in character The second stage is represented by hyperplastic changes and ulceration and the third stage by healing In the third stage fibrous stenosis may result Obstructive lesions show a predilection for the left main bronchus and the right upper lobe bronchus The indications for bronchoscopy in tuberculous patients are clinical and roentgenologic Clinical indications include unilateral wheeze positive sputum without evidence of parenchymal source positive sputum with apparently controlled parenchymal disease severe symptoms (cough difficulty in raising sputum dyspnea and cyanosis) without evident cause in the parenchyma evidence of intermittent retention of secretions such as variation in amount of sputum and occurrence of fever and prolonged fever following thoracoplasty *Roentgenologic indications* include mediastinal shift with or without elevation of the diaphragm hilar flare opaque lesions of lobular lobar or multilobar distribution which may appear suddenly following collapse therapy basal tuberculosis cavities with thin walls and fluid levels or fluctuating in size widespread parenchymal disease without evident parenchymal source and obstructive emphysema Bronchoscopy is contraindicated in terminal phases of the disease and by pulmonary hemorrhage acute respiratory infection and tuberculous laryngitis If the indications are followed in selecting patients about 50 per cent of the bronchoscopies will reveal endobronchial disease

Existence of the preclinical phase of tuberculous bronchitis which can be recognized only by routine bronchoscopy is emphasized When clinical and x ray evidence of

(4) D f Ch t 11 36 58 J F b 194

tuberculous bronchitis is present, a negative bronchoscopy does not rule out involvement of the branch bronchi and examination should be repeated at a future date

The importance of the technic of bronchoscopy in tuberculous patients is stressed with emphasis on the following points careful and complete anesthesia, avoidance of trauma to any bronchial lesion, careful aspiration of all secretions in the tracheobronchial tree during bronchoscopy and just before the bronchoscope is withdrawn, and slow withdrawal of the bronchoscope so that all tracheal secretions which have collected around the scope will be aspirated The patient should be placed on his affected side for three hours after return to bed to prevent secretions being spilled to his good lung durin the time the cough reflex is abolished by the anesthesia

Wilson discusses the pathologic physiology revealed by the bronchoscope and stresses the importance of the bronchial lesion in influencing progress of the parenchymal lesion He considers the stagnation and back firing of secretions the pathogenic factor in producing the opaque lesions basal tuberculosis hilar flares" and disseminated infiltration so commonly seen in the same lung The atomizer effect is the cause of nodular spreads frequently seen in the opposite lung

Local therapy of the endobronchial lesion with 30 per cent silver nitrate has been found effective in lesions considered suitable for treatment, such as the ulcerative and ulcerohyperplastic types, but is only one phase of treatment The general condition and the treatment of the parenchymal lesion are extremely important and should not be neglected Presence of a marked fibrous stenosis contraindicates local therapy except for cauterization of any associated ulceration or granulation tissue Complete thoracoplasty or pneumonectomy is indicated in such cases Dilatation a form of treatment which does more harm than good and leads to delay in applying surgery should be used only to alleviate distressing symptoms Evaluation of the bronchial system is as important as evaluation of the parenchyma No

any of the symptoms signs or roentgen evidence of tuberculous bronchitis should be given any type of collapse therapy without preliminary bronchoscopy The type of collapse therapy to be used for control of the parenchymal lesion is governed by the type of parenchymal disease and the type of endobronchial lesion present

[It may be said that pulmonary tuberculosis always involves the bronchi at least the small branches It is a question therefore of determining when the bronchial lesion influences the clinical progress of the case Careful clinical observation will usually disclose this and indicate when bronchoscopy is necessary This is not always a harmless procedure There are many who now restrict the application of silver nitrate to carefully selected cases and then sparingly —Ed.]

Syphilis and Pulmonary Tuberculosis in the Negro is discussed by Reuben Hoffman and George G Adams (Henryton Md) Of 1 705 Negroes with pulmonary tuberculosis 507 had coexisting syphilis A comparison of this group of 507 with 1 198 with tuberculosis alone revealed no significant differences in the amount of pulmonary involvement predominant type of tuberculous lesion or percentage of deaths in the two groups The difference in percentage of syphilis in the group with minimal and the group with far advanced tuberculosis was less than 7 and could not be used as an indication that syphilis lowered the resistance of a patient to tuberculosis

Antisyphilitic treatment should be given only when prognosis for the tuberculosis is good except in cases of pregnancy or contagious syphilis and then only when certain criteria for treatment are met such as early latent cardiovascular or cerebrospinal syphilis Whether late latent syphilis should be treated is an open question The most important problem in cases in which tuberculosis and syphilis coexist is the potential ability of arsenicals to cause a flare up of tuberculosis In the present series only one case was encountered in which a flare up could be ascribed to use of mapharsen In all other cases in which a flare up occurred during antisyphilitic treatment it could not be ascertained whether it was caused

(5) Am R v Tube 50 85 9 A g t 1944

by an arsenical or other factors or was spontaneous There was likewise no convincing evidence that fractional doses of arsenicals are less likely to produce a flare up than full doses Fractional doses vitiate the aim of treatment which is to "cure" syphilis

Among 239 serologic tests performed on 69 patients with no history or evidence of syphilis false positive reactions occurred only twice

[The power of penicillin to combat syphilis in its early stages is particularly welcome when tuberculosis also exists —Ed]

Erythema Nodosum in Children In reviewing the records of Bellevue Hospital between 1925 and 1938 Edith M Lincoln Janet Alterman and Hyman Bakst[6] found 42 cases of erythema nodosum Patients ranged in age from 2 to 26 years 28 were aged 2–12 All but 3 of the 28 children were white This racial selection is also evident in adults with erythema nodosum Twenty three of the 28 cases occurred during winter and spring In 11 of the 28 cases there was definite evidence of active pulmonary tuberculosis in 7 of these erythema nodosum was associated with onset of primary tuberculosis, and in 4 *the x rays showed active primary tuberculosis but no* evidence of recent onset In 4 of the 28 cases erythema nodosum was associated with acute rheumatic fever and in 1 with acute tonsillitis in the remaining 12 no definite etiology could be established The percentage of positive reactors to tuberculin among the 28 children was 74 that in the children s wards investigated on two occasions, was 25 and 17 respectively

A statistical analysis of all cases of tuberculosis seen in the children's wards and outpatient department at Bellevue Hospital between 1930 and 1938 showed that among 362 children over age 2 with active primary pulmonary tuberculosis there were 13 (3 6 per cent) with erythema nodosum During the same period of 325 consecutive patients with calcified primary *tuberculosis* only 3 had erythema nodosum. Erythema nodosum in children with active tuberculosis is obviously associated with the early phases of the disease

(6) J Ped at 25 311 318 October 1944

Every child with erythema nodosum should be regarded as potentially tuberculous but a positive diagnosis should not be made without a complete study The present review and two others previously published from Boston City Hospital and the children s service of Stanford Medical School indicate that erythema nodosum is uncommon in the United States in comparison with northern continental Europe Most cases in adolescents and adults seen in Boston and New York City are due to infections other than tuberculosis Therefore erythema nodosum may be an important diagnostic aid in the individual case but it cannot be used extensively in differential diagnosis

[Perry (*British Medical Journal* 2 84 847 Dec 30 1944) is in close agreement with this consideration of erythema nodosum He believes there is a diathesis which in part is inherited — Ed.]

Lunula of Finger Nails in Tuberculosis Andrew L Banyai and Anthony V Cadden (Marquette Univ) who previously described a tendency of lunulae to disappear during the course of tuberculosis present observations on 230 additional patients with pulmonary tuberculosis The study revealed that when the disease reaches the moderately advanced and far advanced stages it may cause peripheral circulatory reactions which lead to diminution in size or complete disappearance of the lunulae Average width of the lunulae is definitely less than in normal controls In the moderately advanced stage lunulae are absent in all finger nails 6 times and in the far advanced stage 10 times as frequently as in controls Average width of the lunulae is also significantly smaller in patients with far advanced tuberculosis than in those with moderately advanced disease

Diminished size of the lunulae is explained on the basis of edema of the soft tissues of the distal phalanges which causes partial obstruction of circulation with dilatation of some of the blood vessels and overgrowth of the horn The cause of this local reaction is to be sought in toxic products released by the tuberculous process in

(7) II 1 & C t R 48 30 33 J ly 1944

the lungs and in tissue anoxemia secondary to the decrease in pulmonary respiratory surface area due to tuberculous involvement The high incidence of disappearance of lunulae in patients who have tuberculosis with dyspnea or silicosis with superimposed tuberculosis supports the latter assumption

Modern Views on Primary Pleurisy with Effusion Kenneth Robson[8] finds that the trend is to regard primary pleural effusion as of tuberculous origin unless proved otherwise Other possibilities are (1) postpneumonic effusion after use of sulfonamide compounds, (2) traumatic effusion and (3) effusion in rheumatic infection Factors suggesting a tuberculous origin are a long period of stabilization of the process a relapsing chronic course with recurrent febrile bouts, and involvement serially of both pleural spaces and sometimes of peritoneum Accumulated evidence indicates that the highest incidence of primary pleural effusion is in early adult life Figure 56 taken from the work of Scheel and Foien illustrates the age incidence of primary pleurisy in 957 cases

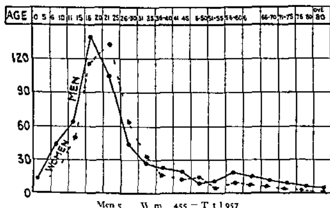
Pleural effusion may occur at or near the time of primary infection or at any other time during the history of the disease In the latter instance it is not usually considered primary If it is assumed that development of pleurisy and later outpouring of fluid is the effect—whether mechanical or due to specific sensitivity—of aggregation of minute tuberculous foci in lung parenchyma or in root glands it will be understood that these foci may be arrested at an early stage and not be recognized during life If there are only one or two aggregations of foci accumulation of fluid will be small explaining *those cases in which fluid is discovered by chance in* absence of ill health

During the primary infective process the patient is in unstable condition and there is danger of aggravation with spread of the infection to other serous surfaces The clinical behavior in some cases suggests that they

(8) Practitioner 153 344 3 3 December 1944

come near acute miliary dissemination Primary effusion carries a 20 per cent risk of pulmonary tuberculosis which usually develops within five years of effusion Treatment is directed toward stabilization of the proc ess

Strict bed rest until temperature has been normal for two weeks is imperative followed by a few weeks of less complete bed rest and then by a period of walking for graded distances Breathing exercises are not advised in early stages and sun bathing may be harmful to an



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Fig 56

unstable patient Except for exploratory aspiration the less done the better especially when the effusion is medium or large Large effusions tend to rapid accumu lations or dangerous redistribution with con equent me chanical effect on pulmonary vessels and mediastinal structures Aspiration cannot be counted on to prevent this and may even predispose to it In the case of medium sized effusions aspiration is indicated for fail ure of absorption after a long period for persistent fever for bronchitis and for asthma

[Pleurisy with effusion should not be treated by art ficial pneu mothorax unless there is an underlying pulmonary lesio for which this treatment obv ously is ne ded —Ed]

Effect of Tuberculous and Sensitized Serums and Serum Fractions on Development of Tubercles in the Chorio Allantoic Membrane of the Chick Emily W Emmart and Florence B Seibert[9] made electrophoretic analyses of the amount of albumin and alpha, beta and gamma globulins present in tuberculous "sensitized" and normal rabbit serums These whole serums and tubercle bacilli of the A27 strain were implanted simultaneously on the chorio allantoic membranes of eight day old chicks The incidence of membranes developing tubercles was calculated and the size and development of the tubercles noted

Fewer tubercles developed when the suspension of tubercle bacilli inoculated contained whole serums high in beta globulin from tuberculous animals or serums high in gamma globulin from sensitized animals, than when it contained whole normal serum The sensitized serums high in gamma globulin content permitted less development of tubercles than the tuberculous serums with high beta globulin content The effect of serums high in gamma globulin while not great enough to prevent tubercle formation completely was sufficient to retard development of the tubercles in the membranes in both number and size during the six day experimental period Electrophoretic analyses of the tuberculous serums used showed that their gamma globulin content was higher than that of normal serums but less than that of serums of the sensitized rabbits Although the action of isolated beta globulin was not studied the data indicate that the gamma globulin fraction rather than the beta possesses the chief tuberculostatic properties

There was a suggestion of partial tuberculostatic effect due to a gamma globulin fraction isolated from pooled serums of patients with minimal tuberculosis although the data were insufficient to be statistically significant

Study of Paratubercle Bacilli Pathogenic Properties are discussed by R Laporte[1] Mycobacterium includes a number of species which aside from their fundamental

(9) J Immu ol 50 143 160 Ma ch 1945
(1) An Inst l st r 6 3 3 5 No ember 1940

quality of acid fastness show other common properties These species are the bacillus of tuberculosis of mammals and birds the bacillus of human and of rat leprosy the bacillus of hypertrophic enteritis of cattle and a group of ubiquitous bacilli lacking spontaneous pathogenicity and designated paratubercle bacilli Although paratubercle bacilli can be frequently isolated from human secretions cases in which they are solely responsible for pathologic lesions are rare Laporte has observed one such case a subcutaneous cold abscess in an infant in which the pus contained a great number of acid fast bacilli that grew rapidly on all mediums including nonglycerinated ones Four cases have been reported in the literature two of subcutaneous abscess one of pleuropneumonia and one of generalized cutaneous eruption All healed spontaneously In the three cases of cold abscess the bacilli were apparently inoculated during a therapeutic injection of a medicament and in the case of the skin eruption during immersion into the sea in the case of pleuropneumonia the source of infection was not known Despite their rarity these cases prove that the paratubercle bacilli normally devoid of any pathogenic power may under certain circumstances multiply in vivo and produce significant lesions

Generally the pathogenicity of paratubercle bacilli for laboratory animals rabbits and guinea pigs is small or nil Certain stocks however can produce slowly developing lesions which have the aspect of nonprogressive tuberculous lesions When such bacilli are injected in an oily medium preferably in paraffin oil they give rise to intensive lesions which progress to massive caseous tuberculosis capable of killing the animal Similar results may be obtained by injecting the bacilli and the paraffin oil separately by two different routes as long is their meeting in the organism (in the lung subcutaneous tissue or lymph nodes) is assured The circulating paratubercle bacilli tend to become fixed and to multiply within the oil deposits in the tissues producing in situ

severe caseous lesions of the same type as do the bacilliferous oil injections Certain nonoily, but irritant, substances, such as aleuron, kaolin or lycopodium powder when injected in combination with paratubercle bacilli are likewise capable of enhancing the pathogenic effect of the bacilli but to a much lesser degree than the oily or fatty substances

The mechanism of action of fat or oil in production of the lesions is not yet clarified Laporte assumes that presence of free fat corpuscles in the tissues creates local physicochemical conditions favorable to the activity and multiplication of bacilli which otherwise without protection of the fatty vehicle are saprophytes The cultures originating in vivo release a continuous flow of toxic substances from the bacillary bodies, which in turn cause mesenchymal reactions The irritant action of the fatty and oily substances per se also plays a role but a minor one

[This and the following article are among the first which have reached this country from France since the close of the war—Ed]

Pathogenic Properties of Dead Tubercle Bacilli in Vaseline Oil Injected by Intratesticular Route According to A Saenz and G Canetti injection of dead tubercle bacilli in vaseline oil intratesticularly into a guinea pig results in metastatic pulmonary lesions which are more marked than those produced by subcutaneous injections These lesions are identical whether human or bovine bacillus is used Intratesticular *injection* of dead bovine tubercle bacilli in the same vehicle into a rabbit results in severe illness with death occurring spontaneously in 30–60 days The lesions produced in the lungs are characterized grossly by hypertrophy caseation and hemorrhagic injection Injection of dead human bacilli into a rabbit is not followed by spontaneous death and the pulmonary lesions are insignificant Injection of avian tubercle bacilli results in pulmonary lesions which are intermediate between the two former types and spontaneous death of the animals is frequent The lesions

(2) Ann Inst Pasteur 13 49 July 1940

produced by each of the bacillary types are comparable to those produced by the corresponding type of living bacilli

Separate inoculation of dead bacilli intravenously and of vaseline oil intratracheally peritoneally or intratesticularly frequently results in pulmonary lesions comparable in every respect to the lesions already described even when inoculation of the bacilli is made 5 10 15 or even 30 days after instillation of the oil

Intratesticular inoculation of dead BCG in vaseline oil into rabbits produces lesions which are only slightly less marked than those produced by dead bovine bacilli from virulent stocks indicating that in chemical and physicochemical constitution BCG is very similar to a virulent bovine bacillus and that the attenuation of living BCG consists merely in marked inhibition of their production Intratesticular inoculation of living BCG in oil suspension produces lesions identical with those produced by dead BCG Likewise the effect on pulmonary tissues of living human bacilli injected in vaseline oil does not differ from that of dead bacilli

Why the intratesticular route favors production of distant lesions to such degree is entirely unexplained Regarding the role of the oil excipient it is suggested that the presence of oil increases the pathogenic activity of dead bacilli in several ways being eliminated from the lungs only with difficulty the oil maintains the bacilli in situ for a long period being largely emulsified in the pulmonary cells it assures intimate contact of bacilli with these cells and it provides a protective shell for the bacilli From the results of the experiments the authors conclude that dead tubercle bacilli retain not only a great deal of the inherent pathogenicity but also that part of it which is specific The virulence of tubercle bacilli can therefore be considered a combination of a pathogenic power specific for the particular animal and exhibited by all bacilli even dead ones and of the capacity to increase exhibited by living bacilli It follows that the attenuation or absence of virulence of

tubercle bacilli for a certain animal species is due either to insufficient pullulation of the bacillary constituent—even in the presence of certain pathogenic power (as in the case of BCG in the rabbit), or to insufficient pathogenic power—even in the presence of active multiplication (as in the case of human bacilli in the rabbit), or to a combination of the two

Some Artefacts Encountered in Stained Preparations of Tubercle Bacilli Diran Yegian and Keith R Porter[3] have demonstrated experimentally that non-acid fast forms appearing in stained smears of young cultures of the tubercle organism are created by the mechanical action of the platinum loop or the spatula used to disperse the organisms Of greatest significance in this demonstration are the facts that (1) preparations made without the mechanical action of spreading instruments failed to show these atypical forms, and (2) the relative abundance of non-acid fast forms in smears depends on the amount of manipulation with the spreading loop or spatula The conclusion reached is, therefore that the non-acid fast granules and fine rods thus revealed are artefacts It also seems probable from the present experiments that the act of sectioning may destroy acid fastness In support of this are the observations (1) that the non-acid fast forms are more abundant where distortion of the paraffin is greatest especially along the marks of nicks or dull places in the knife (2) that the proportion of these atypical forms appears greater in thin than in thick sections and (3) that sectioning and smearing the cultures produce parallel results both procedures yielding a greater proportion of non-acid fast forms from younger material The apparently increased resistance to damage of cells from older cultures is not clear

Enzymes As Factors in Resistance to Tuberculosis Effect of Liver Enzymes on Tubercle Phosphatide Bruno Gerstl Robert Tennant and Oscar Pelzman[4] made tests with extracts of livers obtained from normal

(3) J Bact 48 83 91 July 1944
(4) Yale J Biol & Med 1 455 459 January 194

mice rabbits and guinea pigs Results indicate that mouse liver under full activation splits 90 per cent of the tubercle phosphatide in 48 hours of incubation and the rabbit enzymes 7 07 per cent guinea pig liver accomplishes only half as much as mouse liver Previous studies suggested that the small amount of cleavage demonstrable with the guinea pig organs may be due either to absence of the enzymes essential for cleavage of tubercle phosphatide or to their failure to act because of presence of substances that impair enzyme activity An assay of the phosphatases revealed that the guinea pig liver developed not more than 50 per cent of the phosphomono esterase activity that was noted for mouse or rabbit liver which accounts for the lesser effect of the guinea pig liver on tubercle phosphatide The splitting of both model substrates and of tubercle phosphatide was enhanced by addition of manganese sulfate and magnesium chloride

Among the various chemical fractions of the tubercle bacillus phthiocol because of its oxidation reduction potential was considered a possible inhibitor of enzyme activity In experiments with phthiocol in end concentrations of M/1 250 and M/2 500 25–50 per cent inhibition of monophospho esterase activity was observed None of the three liver extracts revealed any phosphodiesterase activity Liver extracts from immunized rabbits showed a markedly increased ability to split tubercle phosphatide which further suggests that the splitting of tubercle phosphatide represents one of the mechanisms concerned with resistance to tuberculosis

DISEASES *of the* BLOOD *and* BLOOD-FORMING ORGANS, DISEASES *of the* KIDNEY

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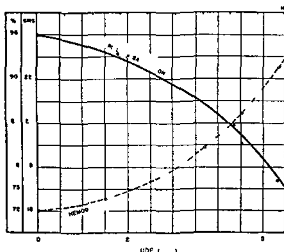
PART III

DISEASES OF THE BLOOD AND BLOOD FORMING ORGANS

GENERAL CONSIDERATIONS

The following articles are concerned with general pathologic physiology or general clinical aspects of blood disorders.—Eds

Influence of Anoxemia on Hemopoietic Activity It has become an almost established fact that oxygen ten



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sion of the circulating blood is important in regulating the degree of hemopoietic activity However most studies of the relation between degree of anoxia and hematologic response at high altitudes have been carried out on human beings or animals subjected for only a few hours

of days to such an abnormal environment, and results obtained in these observations and in short time experiments in chambers where pressure or percentage of oxygen is artificially lowered do not reveal the true nature of the changes

Alberto Hurtado Cesar Merino and Ernesto Delgado[1] (Lima Peru) report investigations concerning morphologic and other characteristics of circulating blood under the influence of temporary, intermittent and chronic anoxic anoxia (anoxemia) Most of the work was carried out at high altitudes and results were compared with those observed in study of healthy subjects at sea level and in previous related investigations The main observations led to the following conclusions

Exposure to a low barometric pressure environment usually causes a polycythemic response There are wide individual variations but in general the level of polycythemia is directly proportional to the degree, duration and continuity of the anoxic stimulus There seems to be a limit for hematologic response to the anoxic stimulus When this is extremely severe a decrease rather than further increase is observed in the resultant polycythemia Interference with formation of hemoglobin may be the responsible mechanism Level of hemoglobin in the circulating blood may be considered one of many factors tending to preserve internal stability or homeostasis against the disturbing influence of a constant lowering of oxygen tension in inspired air Figure 36 shows the relationship between the mean arterial oxygen saturation (per cent) and mean hemoglobin content (Gm /100 cc) in healthy male residents at different altitudes

Polycythemia associated with anoxemia of high altitudes is absolute Elevation in total blood volume which at times reaches high values is due to increased red cell volume Polycythemia observed on arrival at high altitudes apparently is due to factors of release of stored blood and hemoconcentration that corresponding to a

(1) Arch Int Med. 75 284 323 May 1945

repeated or constant exposure to a low pressure environ ment is related to an erythropoietic hyperactivity Polycythemia associated with a constant or intermittent anoxemia tends to show a proportional elevation in the circulating reticulocytes and in serum bilirubin The latter characteristic suggests that an increased rate of cellular destruction parallels increased formation but other factors such as insufficiency of the liver in excre tion of pigment due to the anoxic condition may also play an etiologic role in hyperbilirubinemia

The stimulating influence of anoxemia on the hemopoietic system is restricted to formation of red blood cells and hemoglobin Leukopoietic activity is not af fected and moderate and temporary leukocytosis at times observed on arrival at high altitude is probably related to release and mobilization of stored blood [or to stimulation of the sympathetico adrenal system see the article by Clare *et al* this YEAR BOOK p 290 —Eds]

Chronic anoxemia does not modify erythropoietic ac tivity permanently When a person who has lived since birth at high altitudes is brought down to sea level he shows after some time blood characteristics similar to those found in persons who have always lived under the latter environmental conditions During the early period of adaptation to normal pressure environment there frequently occurs an abnormal decrease in red blood cells and hemoglobin

Comparative study of the polycythemia of high alti tudes and polycythemic processes observed at sea level indicates that (1) in cases of anoxemia at sea level due to pulmonary changes the polycythemic response tends to be less than with corresponding degrees of ar terial oxygen unsaturation at high altitudes except in cases of Ayerza s disease and (2) it is not unlikely that the causative mechanism of polycythemia vera is related to existence of an anoxic stimulus

Depressant Effects of High Concentrations of In spired Oxygen on Erythrocytogenesis Edward H. Reinhard Carl V Moore Reubenia Dubach and Leo J

Wade (Washington Univ) report the effect of continuous inhalation of 70–100 per cent oxygen by four patients with sickle cell anemia for 6–20 days on six different occasions Degree of intravascular sickling was diminished during periods of oxygen inhalation but rate of hemolysis or occurrence of pain was not affected There were definite indications that erythrocytogenesis was depressed On the fourth to sixth day of oxygen administration the reticulocyte level began to fall and several days later red blood cells also began to decrease During three of the six periods red cell counts fell by more than 1 000 000 cells Four or five days after oxygen administration was discontinued, a pronounced reticulocytosis developed and the number of erythrocytes returned to approximately the preoxygen level Congestion of the mucous membrane of the upper respiratory passages anorexia and nausea were the principal evidences of toxic effects produced by high concentrations of oxygen Leukocytes and platelets showed no significant numerical or qualitative change However after oxygen administration was discontinued an increase in the number of circulating leukocytes presumably due to an outpouring from the bone marrow was regularly observed

The authors suggest that the increased oxygen tension produced in the bone marrow by oxygen administration was responsible for the depression of erythrocytogenesis as reflected by decrease of both reticulocytes and red blood cells and that this effect is the physiologic antithesis of stimulation of red cell formation produced by low oxygen tensions

Leukocytosis and the Sympathetico Adrenal System Although leukocytosis has often been linked with excitation of autonomic centers and secretion of epinephrine actual proof for this mechanism is rather inadequate Walterhofer showed that injection of large doses of epinephrine was followed by neutrophilic leukocytosis which he attributed to action of epinephrine on bone

( ) J Cl n I t g t n 3 68 698 S pt mb 1944

marrow Borchardt likewise observed leukocytosis after administration of epinephrine Similar effects may be obtained after injection of parasympathetic stimulants such as pilocarpine and choline Several investigators have presented evidence that leukocytosis may follow stimulation of various parts of the central nervous system These findings and the observation that cold causes leukocytosis are compatible with the assumption that leukocytosis results from excitation of the sympathetic adrenal system To prove this hypothesis F B Clare C H Cress and E Gellhorn[3] (Chicago) performed experiments on vagotomized and adrenodemedullated rats using procedures leading to stimulation of centers of the sympathetico adrenal system i e convulsions induced by metrazol electric shock and paratyphoid vaccine Changes in blood count in vagotomized rats are attributable to excitation of the sympathetico adrenal system whereas those in adrenodemedullated rats indicate involvement of the vago insulin system

Convulsions induced by metrazol and electric shock caused in every vagotomized rat a neutrophilic leukocytosis reaching a maximum in 18–24 hours and averaging 115 per cent No leukocytosis was found in adrenodemedullated animals These facts suggest that leukocytosis results from liberation of epinephrine following excitation of sympathetic centers by these procedures No evidence could be found for an influence of the vago insulin system on the blood picture The relatively long latent period and persistence of leukocytosis and its neutrophilic character point to the bone marrow as the site of action of the liberated epinephrine

Other conditions such as anoxia and emotional excitement which lead to a sympathetico adrenal discharge may likewise cause leukocytosis in this manner There are however complicating factors Experiments with typhoid paratyphoid vaccine injections produced leukocytosis in both vagotomized and adrenodemedullated animals with a maximal effect after 10 hours indicating

(3) A I t M d 1 653 661 O tob 1944

that the sympathetico adrenal discharge is not the only factor responsible for the leukocytosis The leukocytosis cannot be the consequence of fever, since previous experiments had shown an increase in temperature in the normal and a decrease in adrenodemedullated animals after typhoid paratyphoid vaccine The results suggest that typhoid paratyphoid vaccine acts on the bone marrow directly possibly in addition to its action on the sympathetic centers

Quantitative Determination of Serum Bilirubin with Special Reference to Prompt Reacting and Chloroform Soluble Types Hector Ducci and Cecil James Watson[4] (Univ of Minnesota Hosp) recommend a slight modification of the Malloy Evelyn technic for serum bilirubin determination which facilitates estimation of the prompt and delayed direct reacting types as well as the total bilirubin Nearly all the bilirubin in body fluids from subjects with mechanical jaundice gives rise to azobilirubin formation within one minute at which time the delayed direct reacting type has not yet begun to produce color The reading for the prompt direct reacting bilirubin is consequently made at one minute after addition of reagent to the diluted serum The total direct reacting bilirubin is read at 15 minutes The difference between the 1 and the 15 minute reading represents the delayed direct reacting bilirubin Reading for total bilirubin is made 15 minutes after addition of alcohol The difference between this and the reading for total direct reacting bilirubin represents the indirect bilirubin

The authors compare results of this modified Malloy Evelyn method with those of the Sepulveda Osterberg procedure The bilirubin extracted from the serum by chloroform according to the latter method is not equivalent to either the indirect reacting or the delayed direct reacting bilirubins In most instances it is less than either and in all instances much less than the sum of the two The lower values obtained by chloroform

(4) J Lab & Clin Med. 30 293 300 Ap 1 1945

extraction are due to incomplete extraction Since the delayed direct and the indirect fractions are believed to have identical significance chloroform extraction is held to be inadequate and superfluous

With s objection to the Malloy Evelyn method based on the assumption that methyl alcohol has a weaker catalytic activity than caffeine sodium benzoate has been found to be valid only for the alkaline solution used by With and not for the solution prepared by the Malloy Evelyn technic and used in the present study

Conversion of Hematin to Bilirubin Following Intravenous Administration in Human Subjects The question whether hematin once formed under abnormal conditions is capable of conversion to bilirubin in vivo is of considerable fundamental significance because of presence of hematin in the circulating blood in various pathologic states such as gas bacillus sepsis pernicious anemia hepatic disease severe malaria and blackwater fever Certain investigators particularly Bingold and Duesberg recently dissented from the view that hematin is converted to bile pigment

In experiments on 11 subjects I J Pass S Schwartz and C J Watson[5] (Univ of Minnesota Hosp) found that following intravenous administration of hematin in nonjaundiced human subjects an augmentation of feces urobilinogen occurred which was roughly proportional to the amount of hematin given This is interpreted as evidence of formation of bile pigment from hematin Serum bilirubin was not uniformly elevated following hematin injections in contrast with those of hemoglobin which regularly produced sharp rises Nevertheless significant elevations were noted after administration of hematin in numerous experiments A relatively slow conversion of hematin to bilirubin is suggested by the long persistence of hematin in the circulating blood This may be related to formation of methemalbumin Increased excretion of bilirubin in the

(5) J Clin Investigation 24 283 91 May 1945

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(4) J Lab & Clin Med 30 293 300 Apr il, 1945

myocardial infarction and marked atherosclerosis of the coronary vessels were demonstrated In one case a thrombus was superimposed on a ruptured intimal plaque In two cases no actual point of complete occlusion of the artery could be demonstrated In two cases bleeding was due to duodenal ulcers Gastric ulcers were present in the other two

All patients in whom cardiac failure followed hemorrhage were over 60 Autopsy showed atherosclerosis of coronary vessels without myocardial infarction and there was clinical and anatomic evidence of cardiac failure either initiated or increased by hemorrhage Five patients had bleeding gastric ulcers and one had a bleeding duodenal ulcer

Whenever there is severe coronary sclerosis the myocardium suffers from an actually or potentially inadequate blood supply Physiologically it is obvious that anything resulting in reduction of ability of the blood to carry oxygen—reduction in blood volume hemoglobin content or number of red cells—or in reduction in blood pressure forcing blood through a narrowed coronary tree is bound to cause a sudden increase in this inadequacy Hemorrhage regardless of origin if severe enough will produce anemia lowered blood pressure and some shock It might therefore be expected to lead to signs of decompensation of arteries already having difficulty carrying out their function Hemorrhage also tends to produce tachycardia which increases oxygen need and probably in itself reduces coronary circulation in relation to volume output

A frequent but undiagnosed cause of hemorrhage in older patients is erosion of a blood vessel resulting from duodenal or gastric ulcer Hemorrhages are apt to be severe because the eroded artery itself is sclerotic and therefore does not easily collapse and thrombose Hence symptoms of inadequate coronary circulation follow such hemorrhages Why in some cases actual thrombosis is found is perhaps harder to understand A high percentage of thrombosis in older patients

urine may partially account for failure of serum bilirubin to rise after hematin injections in subjects with complete biliary obstruction

Artificial Production and Significance of Target Cells are discussed by William N Valentine and J V Neel (Univ of Rochester) with special reference to their occurrence in thalassemia (Cooley's anemia)

Red blood cells in stained smears which exhibit a peripheral ring and a central dot of hemoglobin have been termed from this appearance "target cells" Such appearances may be produced in vitro by suspending normal erythrocytes in plasma or serum rendered hypertonic by addition of chemicals or by evaporation Severe rapid dehydration of a dog, with attendant plasma concentration resulted in a slight but significant increase in the number of target cells in the peripheral circulation Naturally occurring target cells in a pathologic condition, sickle cell anemia may be converted to cells of relatively normal appearance by suspending them in the patient s own plasma rendered hypotonic by dilution with distilled water

The target cell is considered to be a cell whose envelop is large in relation to its contents regardless of the cause of this relationship Its wide distribution in a hypochromic group of anemias which respond to iron and in hypochromic anemias thalassemia major and minor which do not respond to iron suggests the possibility that the latter may be due to iron deficiency This deficiency may be due to some inherited inability to metabolize completely to hemoglobin more than a limited amount of iron

Cardiac Failure Associated with Acute Anemia Thomas D Kinney and G Kenneth Mallory[7] describe four cases in which actual infarction of the myocardium was present and six cases in which heart failure followed hemorrhage Autopsy was performed in all cases All cases in the first group were similar in that

(6) Am J M S 209 741 75 June 1945
(7) New Engl nd J M d 3 15 18 F b 2 1945

and under such circumstances successful surgical removal is followed by a dramatic restoration of normal hemolytopoietic equilibrium

Knowledge of the functions of the spleen will enable one to predict and be prepared to recognize certain pathologic states dependent on corresponding splenic dysfunctions The vascular system of the spleen is made up of arteries veins and sinusoids which serve admirably as a reservoir for blood cells and plasma Pathologically there may be congestion of this system with splenic enlargement and excessive sequestration of plasma and cellular elements secondary to myocardial failure bacterial toxemia or hepatic cirrhosis with portal hypertension The spleen is a lymphatic organ with typical lymph sinuses and follicles the germinal centers of Fleming reflecting normal lymphopoiesis Lymphocytes are not simply precursors of other blood cell types Probably they have to do with endogenous protein metabolism in addition to their defense function as infiltrative elements surrounding foci of infection in tubercles chronic abscesses and perhaps less obvious tissue reactions The lymphatic portion of the spleen is involved in hyperplastic reactions chronic lymphatic leukemia serum sickness and other types of miscellaneous protein intoxications and sensitizations The third and perhaps most significant and important structural and functional element in the spleen is the so-called reticulo endothelial system of phagocytic cells consisting of endothelium and reticulum The reticulum gives rise to other reticulum cells and to primitive cells from which monocytes differentiate and mature Reticulum cells are mesenchymal rest elements in adult tissues with embryonic potentialities This complement of embryonic or potentially developmental mesenchymal tissue in the spleen may lead to ectopic blood formation under certain pathologic circumstances The specific endothelial cells have a marked phagocytic capacity in situ and as free desquamated clasmatocytes There is vidence that these reticulo-endothelial cells also par

develops from rupture of an atheromatous focus into the lumen of a blood vessel Sudden changes in arterial blood pressure may possibly account for rupture of an atheromatous abscess through the thin endothelial cover into the lumen and may thus lead to thrombosis Severe hemorrhage therefore appears to be more hazardous for the atheromatous subject than for a person with normal arteries

Therapeutically any means that will combat both profound anemia and a serious drop in blood pressure apparently is indicated but care must be taken because the same means used to prevent thrombosis in the coronary circulation may be similarly effective in the vessel producing the original hemorrhage Blood transfusion apparently is the treatment of choice since red cells and circulating fluid are thus replaced Glucose and saline solutions intravenously should be used sparingly since they tend to reduce unit oxygen carrying capacity of the blood while putting additional strain on the heart

These cases indicate the danger of having an elderly arteriosclerotic patient serve as a blood donor These cardiac complications are also likely to occur in elderly patients with traumatic shock or hemorrhage and preventive means should always be instituted

Differential Diagnosis and Treatment of Diseases Involving the Spleen are discussed by Charles A Doan[8] (Ohio State Univ) Bone marrow and lymph nodes are especially concerned with the origin of circulating blood cells The spleen serves as a reservoir for these cells and as a conservator and storage depot of elements important for hemogenesis In these roles the spleen becomes a potential pathogenic agent—an organ that can mimic, and can simulate in its pathologic control and destruction of circulating blood elements any failure in cellular production by bone marrow Enlargement of the spleen is frequently accompanied by a pathologic accentuation of one or more of its physiologic functions

(8) West Virgini M J 41 121 129 May 1945

sometimes lifesaving in an acute hemolytic crisis Whether the preoperative red cell count is 700 000 or 4 000 000 the results have been equally satisfying and permanent

An acute crisis of thrombocytopenic purpura is also a major medical emergency requiring exact differential diagnosis The sternal bone marrow should show megakaryocytic hyperplasia with many young megakaryocytoblasts The adrenalin test may or may not reveal splenic hypersequestration of platelets Recovery of red cells in a purpuric patient after splenectomy parallels that in patients with hemolytic erythroclastic crises With increase in blood platelets which immediately follows operation all hemorrhages cease and the hyperplastic bone marrow quickly re establishes the red cell equilibrium Splenectomy also produces satisfactory results with disappearance of all hemorrhagic tendencies and increase of platelets which is maintained permanently [This is decidedly too optimistic a prognosis for the effect of splenectomy in most series of cases of thrombopenic purpura —Eds] The spleen should not be removed in allergic or anaphylactoid purpuric states rather blood transfusions should be given if necessary and the offending antigen searched for and eliminated Examination of the bone marrow will frequently reveal toxic damage to megakaryocytes and time must be given for elimination of the foreign antigen and development of a new replacement generation of these mother cells

Banti s syndrome is characterized in the so called third stage by splenomegaly portal cirrhosis with or without ascites and leukopenia If hepatic function is not too greatly impaired splenectomy should be considered Splenic artery ligation may occasionally need to be substituted for splenectomy If and when the spleen can be removed a normal cellular equilibrium is re established and further medical management may be more successfully accomplished The earlier in the disease the spleen is removed the safer and better

ticipate in the process of producing antibody globulins

The two types of phagocytic cells in the spleen under normal physiologic conditions rid the blood stream of cellular and bacterial debris The phagocytic capacity of these cells however is susceptible at times of excessive pathologic destruction of normal cellular elements particularly in individuals with a congenital predisposition to hyperfunction of this organ In congenital hemolytic icterus the red blood cells become the chief victims of splenic destruction Blood platelets are more or less selectively attacked in thrombocytopenic purpura haemorrhagica of splenic type Doan and his co worker have differentiated primary splenic neutropenia from Banti s syndrome in which the spleen more or less specifically destroys the neutrophilic granulocytes Despite an obvious heroic effort by bone marrow to compensate by producing vastly increased numbers of neutrophilic granulocytes the spleen keeps their level in the circulating blood and therefore the supply to the tissues at a minimum so that infection of pathologic significance may develop at any susceptible site

If the spleen can under certain circumstances selectively sabotage red cells granulocytes or platelets then in some individuals the organ might be expected to fail entirely to discriminate between elements passing through it resulting in a pansplenic hematocytopenia simulating hypoplastic anemia but without inadequacy of the bone marrow to produce these elements Actually in such patients a tremendous compensatory hyperplasia of all bone marrow elements has been found

In congenital hemolytic icterus accumulated evidence points clinically and histopathologically to the reticulo endothelial cells of the spleen as the fundamental fault since this type of anemia can be permanently cured by removal of all splenic tissue Doan advocates prophylactic splenectomy to avoid erythroclastic crises and formation of pigment gallstones in cases definitely diagnosed and showing any signs of activity SJ

TRANSFUSION OF BLOOD AND BLOOD SUBSTITUTES

The first abstract is of an article summarizing the important work of Cohn and his associates on the chemical fractionation of human plasma in connection with a search for improved blood substitutes including salt free albumin and certain useful globulin fractions of plasma as concentrated isoagglutinins certain immune globulins fibrinogen and others Many of the articles in this chapter deal with the subject of the Rh property This topic is complex because of the several Rh factors now recognized the lack of adequate amounts of certain types of anti Rh typing serums and the presence of the so-called blocking antibodies These subjects discussed below in many aspects are distinctly a problem for the special laboratory However from the articles presented the reader can gain a general acquaintance with the present status of the subject.—Eds.

Blood Proteins and Their Therapeutic Value are discussed by Edwin J Cohn[9] (Harvard Univ) Whole blood and plasma were well known therapeutic agents before World War II and their value has been further proved in military practice Whole blood is especially needed when there has been severe blood loss or when severe loss is anticipated in major operations Red cells are also needed to combat the anemia which frequently occurs in convalescence from wounds

Progress in preservation of red cells both in whole blood and in mediums in which they can be resuspended may be expected to continue at an accelerated rate because of new methods and new knowledge Resuspended red cells can probably be used for many conditions for which whole blood transfusions are employed Injection of plasma or of a plasma fraction may be satisfactory in others The social economy of using cells and plasma separately in therapy of different conditions if either can be demonstrated to be as satisfactory as whole blood is advantageous enough to demand future consideration

Plasma has been used chiefly for prevention and

(9) S I 101 51 56 J 19 1945

Primary splenic neutropenia, a subgroup of Banti's syndrome may be chronic, subacute or acute Profound neutropenia with splenomegaly, but without demonstrable liver damage are the principal diagnostic criteria plus marked nonleukemic myeloid hyperplasia of bone marrow There are oral ulcerations, chronic infections and abscesses reflecting the deficit in granulocytic cell defense Differential diagnosis lies between primary splenic neutropenia and Banti's syndrome Felty's syndrome malignant neutropenia and subleukemic leukemia There are portal hypertension and liver cirrhosis in Banti s syndrome In Felty s syndrome, neutropenia is usually less severe and there are joint disturbances with splenomegaly In malignant neutropenia, there are usually a history of antigenic drugs absence of splenomegaly and toxic damage to the bone marrow particularly to neutrophilic myelocytes In subleukemic leukemia, if the blood picture does not show pathognomonic qualitative cellular changes the bone marrow will be hyperplastic with leukemic elements Splenectomy produces prompt and striking relief

When any physiologic function of the spleen becomes accentuated pathologically serious consideration should be given to its prompt removal particularly in more acute syndromes The pathologic spleen may at times constitute a real threat to health and actual survival The leukemic states are an exception to this generalization The spleen is not apparently, essential to maintenance of life or health at any age and therefore may be removed without prejudice to future hemolytopoietic equilibrium and longevity

systematic scientific investigation The first is concerned with removal of depressor substances which have heretofore prevented intravenous use of gamma globulin concentrates The second concerns separation of gamma englobulins of the plasma from iso agglutinins (blood typing globulins) cholesterol and carotenoid bearing beta globulins so that clinical investigations with this potential source of antibodies may also be begun

The fractionation process developed by Cohn yields all components of human plasma in five major fractions The number has purposely been made small to facilitate and render economical large scale processes Separations depend on principles determining electrostatic interactions between proteins and neutral salts which generally lead to increased solubility and interactions with less polar organic liquids which generally lead to precipitating action The balance between these forces has made possible definition of conditions leading to far sharper separations than previously were possible When the method is applied to plasma the fibrinogen which is the structural element of the blood clot is concentrated in fraction I Fractions II and III contain essentially all the prothrombin which converted to thrombin transforms fibrinogen into fibrin all the immune globulins for which tests have been made the isohemagglutinins and Rh antibodies of value in blood grouping as well as all the carotenoids and such part of the cholesterol and phosphatides of plasma as appear to be associated with beta rather than alpha globulins the midpiece of complement and probably innumerable other components of plasma not yet recognized The remaining globulins are concentrated in fraction IV and these have recently been subdivided into two fractions In this process all proteins in plasma concerned with the coagulation process are concentrated in fractions I and III 2 the immune globulins in II and III 1 the lipoproteins in III 1 and IV 1 and the albumin in fraction V

Control of infectious diseases by passive immuniza

treatment of shock which in military medicine generally results from rapid decrease in volume of circulating blood due to loss of blood and plasma proteins externally and into damaged tissues As they cannot readily pass through the kidney the injected plasma proteins increase the body's reservoir of plasma proteins and as they do not readily traverse the capillary walls they increase the plasma volume by drawing water from the tissues into the blood stream Controlling the equilibrium between water and electrolytes in blood and tissues is largely performed by albumins, although all dissolved colloids will exert some osmotic effect

Albumins of plasma represent less than 60 per cent of plasma proteins but are responsible for nearly 80 per cent of osmotic efficiency of plasma on which its value in treatment of shock largely depends Unlike plasma albumin is so stable that it can be dispensed in solution the albumin molecules are so symmetrical that a 25 per cent solution is isoviscous with whole blood. The iso electric salt free albumin is prepared as a dry, white powder it can be redissolved at any concentration and with any diluent As a concentrate poor in salt it is proving valuable as a diuretic agent

A large scale public health experiment has now supplemented earlier clinical studies in demonstrating the value of the gamma globulins of human plasma in modification or prevention of measles These have been separated from the same plasma which yielded the albumin employed in prevention and therapy of shock Gamma globulin constitutes about 11 per cent of plasma proteins two fractions may be separated one richer in euglobulin and the other in pseudoglobulin The latter fraction represents about 5 per cent of plasma proteins and contains the antibodies effective in modification or prevention of measles as well as antibodies for several other virus diseases

Two chemical problems have thus far limited studies to determine the most effective use of gamma globulins progress being made suggests that both are 1 to

than is obtained now when no attempt is made to select high titered plasmas Titers of pooled plasmas processed have varied from 1 32 to 1 128 and those of the final products from 1 512 to 1 2048

Two methods of assay speed and intensity of agglu tination (avidity) and antibody content (test tube titer) have been used to determine isohemagglutinin activity

A purified euglobulin fraction of plasma in which isohemagglutinin activity is mainly concentrated may be dispensed in a dried stable state The powder dis solves readily on addition of proper amounts of distilled water and is highly active for blood grouping The separated isohemagglutinin containing globulins repre sent about 5 per cent of proteins present in plasma Electrophoretically this protein fraction is composed mainly of gamma and beta globulins No chemical or physical differences have been encountered between anti A and anti B isohemagglutinins The isohemagglu tinins in plasma have been concentrated approximately 16 times over plasma an almost quantitative yield

Polyvinyl Alcohols As Blood Substitutes N W Roome Lawrence Ruttle Leverne Williams and Ward Smith (Toronto) examined several members of the polyvinyl alcohol series to determine their suitability as colloids for a blood or plasma substitute Of these PVA RH623 appeared suitable as a plasma substitute Its es sential physical properties closely resemble those of plasma proteins and it appears innocuous to the recipi ent After acute hemorrhage in dogs it maintained blood pressure as well as similar blood transfusions It is lost from the blood stream in dogs at about the same rate as plasma proteins regenerate It did not appear antigenic These features if further confirmed make it appear nearly ideal as an inert plasma substitute

Inert substitutes have certain inherent disadvantages They do not promote wound healing or act as foodstuffs as a protein might They do not contribute to hemostasis

( ) C d M A J 51 93 299 O t be 1944

tion with gamma globulins may well be the largest need of a civilian population for a blood derivative In fractionation of blood to obtain the gamma globulins the red cells and other plasma proteins become available for therapeutic uses albumin for treatment of shock hypoproteinemia and edema and, prepared in the salt poor condition, as a diuretic agent fibrin foam and thrombin as a hemostatic agent, fibrin film as a substitute for a natural body membrane and the large number of other cellular protein and lipid components whose physiologic function and chemical nature are only beginning to be explored for whatever therapeutic purposes may prove most important

Chemical and Immunologic Studies on Products of Human Plasma Fractionation Separation and Concentration of Isohemagglutinins from Group Specific Human Plasma According to L Pillemer, J L Oncley M Melin J Elliott and M C Hutchinson[1] (Harvard Univ) specific high titered grouping serums are necessary for accurate blood grouping Collection of high titered serums from special donors has previously been the chief means of procuring such serums Recently need for large quantities of potent grouping serum and difficulties in obtaining donors with sufficiently high titered serum isohemagglutinins led to investigation of the possibility that chemical or physical concentration of plasma from random donors of proper group might provide a sufficient quantity of uniform high titered grouping material

The isohemagglutinin activity of fraction II plus III obtained as a by product in fractionation of human plasma for production of serum albumin had been shown previously The initial step in preparation of an isohemagglutinin-containing fraction from human plasma involves collection of blood from donors of a single group, either A or B for a given pool Initial titration of each plasma to exclude those of low titer would lead to a much more potent grouping material

(1) J Cl Investigat n 23 50 553 July 1944

Thermal tests have demonstrated that anti Rh agglutinins react as a rule best at 37 C and in most instances the titer drops precipitously with the temperature The thermal behavior of anti A and anti B agglutinins is strikingly different from that of anti Rh agglutinins Their titer is usually highest at icebox temperature and decreases as temperature rises

Some serums with anti Rh agglutinins fail to react in undiluted serum but become manifest in higher dilutions This is known in other forms of antigen antibody reactions as the prozone phenomenon Wiener demonstrated recently so called blocking antibodies as the cause of the prozone effect These antibodies combine with the red cells but do not clump them They are independent of agglutinins and may interfere with agglutination The practical significance of this is that anti Rh agglutinins may be overlooked occasionally if only undiluted serum is tested Therefore dilutions up to 1 20 should be used

Blood obtained 8–20 days following childbirth is more likely to contain agglutinins than that obtained before or after that period During the same period titers of agglutinins are more likely to be higher Absence or lower titers of agglutinins during the first days after delivery may be due to neutralization by antigenic substances of the fetus Their elimination is followed by a rise of specific antibodies Anti Rh agglutinins were found in 82 of 152 Rh negative mothers of children with erythroblastosis

It has been known for decades that erythroblastotic infants do not thrive on their mothers milk Finding of anti Rh agglutinins in breast milk furnishes an explanation Davidsohn found them in sizable titers in a majority of specimens of milk examined

Only nine of the mothers of erythroblastotic infants were Rh positive Incidence of Rh positive women may be even smaller because autopsies in four of six cases showed certain changes which necessitated classifying these cases as atypical forms of erythroblastosis In two of three mothers the exact Rh blood type was not de

by clotting large amounts would be expected to impede clotting by diluting the fibrinogen However their non protein nature lessens the likelihood of anaphylacti reactions They obviously do not provide antibodies and erythrocytes and hence are valueless in anemias and infections except to improve peripheral circulation

If limited to its proper field of usefulness this type of polyvinyl alcohol would appear desirable as a first treatment for hemorrhage or shock assuming that hemostasis can be obtained or that direct bleeding is not a prominent feature Its small cost relative ease of preparation and stability in storage would permit keeping it available for emergency use in amounts larger than can be economically kept in a blood or plasma bank

Solutions of 4 per cent polyvinyl alcohol RH623 were administered to four human subjects in amounts of 125 420 430 and 480 cc respectively No untoward subjective or objective effects were noted After the three larger doses dilution of blood occurred and persisted appreciably for 24 hours

[The rest of the articles in this section are concerned with the theoretical and practical aspects of the Rh property—Eds]

Heredity of Rh Blood Types Observations on Relation of Factor Hr to Ph Blood Types are presented by Alexander S Wiener (New York City) I Davidsohn and E L Potter[3] (Chicago)

Rh Antibodies are discussed by I Davidsohn[4] (Mt Sinai Hosp Chicago) The Rh factor is a permanent and static constituent of the blood Rh antibodies are absent normally when present they are always due to immunization and are therefore subject to the many influences which affect immunization Possibly eventually various forms of Rh antibodies will be discovered as in other antigen antibody reactions but thus far only agglutinins are known Rh hemolysins have not yet been demonstrated in vitro though the clinical significance of Rh incompatibility is based on hemolytic action of Rh antibodies in vivo

(3) J E p r Med 81 63 2 J ry 194
(4) Am J Cl Path. 15 9 10 M h 194

that failure of an Rh positive blood to be clumped by it indicates that it belongs to a homozygous Rh positive person However there are reasons to doubt that Hr antiserum can differentiate homozygocity from hetero zygocity

Significance of Rh Factor in Medicine and Obstetrics is discussed by D F Cappell[5] The Rh factor is not a single group specific substance but consists of seven closely related factors already identified while existence of an eighth variety is postulated Study of transfusion reactions indicates that the Rh factors are only occasion ally strongly antigenic in man and that iso immunization to them is usually slow in onset A minority of Rh nega tive persons rapidly become sensitized to Rh positive blood administered intravenously but a serious reaction does not occur with a first transfusion in the absence of previous sensitization

In pregnancy also iso immunization to the Rh factor occurs in only a minority of women exposed to the risk and the great majority fail to become immunized by fetal Rh antigens which they themselves lack It is not clear whether this is due to inherent insusceptibility of the mothers or to failure of fetal antigen to gain entrance to the maternal circulation but by analogy with transfusion reactions probably insusceptibility is mainly responsible Nevertheless iso immunization may appear only after a long series of successful pregnancies and hemolytic dis ease of the fetus may first be observed only after 10 or more normal children have been born Evidence at pres ent available indicates that hemolytic disease of the new born is due to iso immunization of the mother against a fetal antigen which she lacks and that the Rh antigen is that most often concerned

Treatment of hemolytic disease of the new born con sists of intravenous transfusion of blood compatible with the mother s serum on the basis that the transfused red cells must remain in the infant s circulation unaffected

(5) Gl sg w M J 4 1 5155 N mber 1944

termined but their blood reacted with only one of three anti Rh test serums Both had anti Rh agglutinins These two cases represent erythroblastosis due to Rh incompatibility to one of the special Rh factors in women who though Rh positive differed in Rh blood type from their husbands and children

Wiener s classification of Rh blood types is based on existence of three varieties of anti Rh agglutinins One

RH SUBGROUPS

Rh Antiserums				Approximate incidence %
A ti Rh_o 85% I o	A ti Rh 70% I os	Anti Rh 30% I os	S bgroup	
—	—	—	Rh neg	1° 4
—	+	—	Rh	0 8
—	—	+	Rh″	0 5
+	—	—	Rh_o	2.0
+	+	—	Rh	53 6
+	—	+	Rh	11 4
+	+	+	Rh Rh	16 8

clumps about 85 per cent of blood specimens from white individuals collected at random (*serum anti* Rh_o), the second agglutinates about 70 per cent (serum anti Rh′) and the third reacts with *only about 30 per cent* (serum anti Rh′) Seven blood types resulting from a combination of reactions and their approximate incidence are shown in the table More Rh types are known but are not included because they are rare One practical application of expanding knowledge of Rh blood types is that finding a mother of an infant with erythroblastosis to be Rh positive does not necessarily exclude Rh incompatibility as the cause of the disease Thus it is possible to explain almost all cases on the basis of the Rh factors

Levine was the first to report an atypical agglutinin in an Rh positive mother of an infant with erythroblastosis It clumped the blood of all Rh negative and of some Rh positive persons He called it anti Hr agglutinin British authors claim that their serum clumps all Rh negative and only heterozygous Rh positive persons and

women giving a history of transfusions preceding their first full term pregnancies with Rh positive fetuses and (2) a control group not immunized previously by transfusions (see Table) This disclosed that erythroblastosis

ERYTHROBLASTOSIS FOETALIS IN FIRST BORN OF RH NEGATIVE WOMEN

	Transfusion History	
Severity of Disease	+	—
Mild	1	4
Severe	5	4
Fetal death	10	1
No of cases	16	9

foetalis is almost twice as common in Rh negative women previously immunized by transfusions still more striking is the high incidence of fetal death

These observations support the recommendation that no transfusion be given to young women girls or even female infants unless tests for Rh are performed All those found to be Rh negative must receive Rh negative blood One or more transfusions of Rh positive blood administered to an Rh negative female infant may prevent her many years later from having one or more normal Rh positive infants

The question arises as to the mechanism responsible for erythroblastosis foetalis in the first born in the absence of previous transfusions Presumably this group of Rh negative mothers was selected because of their readiness to respond by antibody production The possibility exists however that immunization in these women may have been initiated many years previously by the common practice of administering blood intramuscularly particularly to the new born Usually it is difficult to obtain such a history but in view of this routine and indiscriminate practice in the past this procedure must be seriously considered as the source of iso-immunization in Rh negative individuals It is necessary to avoid this form of therapy in Rh negative girls or women unless Rh negative blood is used

by any abnormal antibody derived from the mother In 90 per cent of cases this means Rh negative blood but in the remaining 10 per cent in which the mother is Rh positive the maternal blood is the only safe guide and Rh negative blood may be dangerous Treatment by transfusion should be given as soon as possible without waiting for signs of hemolytic disease to develop Examination of blood from the umbilical cord and of the mother's blood will establish diagnosis at once in most cases

Blood transfusions should be given to women of child bearing age only after taking account of the Rh factor Women admitted into maternity and gynecologic departments as emergencies on account of hemorrhage should not receive whole blood until Rh tests have been made Plasma should be given to tide the patient over the emergency until blood of proper Rh type can be obtained

Prevention of Unintentional Iso Immunization of Rh Negative Female Population Philip Levine[6] (Linden N J) states that prevention of iso immunization of the Rh negative female population including even the new born by transfusions with Rh positive blood is important Even the first born is frequently lost as a result of previous immunization by transfusion Indications are that once an Rh negative individual is immunized that person remains immunized for the remainder of his or her natural lifetime Although immediate evidence of iso immunization the presence of Rh antibodies is evanescent, the tissues responsible for production of antibodies i e cells of the reticulo endothelial system are capable of responding far more rapidly to the same immunizing stimulus even many years after the initial response Immune antibodies are demonstrable only for comparatively short periods in contrast to the immunized state which persists for many years and must be considered permanent

Levine analyzed the frequency of erythroblastosis foetalis in the first born of two groups of subjects (1)

(6) J A M A 1 8 946 July 3 1945

positive blood by transfusion Mothers who have had an erythroblastotic child or had antibodies in their serum have little chance of having additional normal Rh positive children Later children if Rh negative (by another husband or heterozygous husband) would not be affected regardless of anti Rh titer

If some risk is incurred it may well be justified in view of possible lifesaving service rendered e g 325 cc serum from one of the authors two volunteers because of its high titer can perform over 250 000 tests if used at a conservative dilution of 1 40 assuming 20 tests per cc serum The problem of producing sufficient anti Rh testing fluid for routine testing thus appears largely solved Furthermore use of a strongly reacting testing fluid makes this admittedly delicate test easier to read

Results obtained by injection of such small amounts of Rh positive blood (7 and 10 cc) indicates that the Rh factor may behave as a reasonably strong antigen under suitable conditions In view of the reaction in one volunteer to 5 cc the authors believe larger doses should be used with extreme caution although in this instance the reaction may not have been due to hemolysis In choosing red cells to inject it seems that cells of the infant which has caused the immunization would be most certain to produce further antibodies However it may be difficult to obtain these cells and they may be greatly diluted with transfused Rh negative blood if the infant has been treated for erythroblastosis An alternative would be to use the father s cells if otherwise compatible or to use Rh positive erythrocytes which have been demonstrated to react most strongly with antibodies already present in the mother s serum (i e cells of same specificity e g Rh_0 cells for Rh_0 antibodies)

In testing titers of Rh antiserums the same cells should be employed that were used as the antigen For determination of the end point of titration precise measurement of the dilution should be made using accurate pipets or burets and starting the initial dilution at a fairly high value

The so called biologic test to detect Rh incompatibility will also serve to immunize

Unintentional immunization of the Rh negative female population by transfusion or intramuscular injection of Rh positive blood can now be prevented This simple measure by itself should reduce the incidence of erythroblastosis foetalis, especially in its more severe forms

Preparation of Potent Anti Rh Typing Serums by Injection of Rh Positive Blood into Previously Iso Immunized Individuals is described by Joseph M Hill Sol Haberman Alfonso Velez Orozco and Shirlie Tallal Truby[7] (Dallas Tex) The need for using human sources for Rh antiserums arose from the fact that sufficiently potent serums are difficult to produce in animals, are small in quantity and because of low titer cannot be increased appreciably by dilution By contrast antiserums from mothers of infants with hemolytic disease have often proved very satisfactory It seemed logical to go a step further and by intravenous injection of Rh positive cells to raise the titer of serum from mothers of erythroblastotic infants This could be done either shortly after delivery to produce higher titers or at later intervals to produce satisfactory antiserums through the anamnesic reaction Obviously possible risks incurred by such blood donors had to be carefully weighed and the decision made in consultation with the patient on an individual basis

Because of possible serious consequences of Rh iso immunization it is believed that only those persons previously iso immunized (through pregnancy or prior transfusions) should be chosen for production of Rh typing serums by injection of Rh positive cells Risks of possible transfusion reactions which would be incurred by injection in Rh negative volunteers not previously sensitized probably are not justified On the other hand little if any, additional danger is added by increasing the antibody titer These sensitized individuals in any event should be warned against ever receiving Rh

(7) J A M A 1 9 944 946 July 3 1945

substances of specificity Rh_0 Rh and Rh were demonstrable i e they interfered with the action of these specific antiserums These inhibitor substances of specificity Rh and Rh are similar in behavior to that of specificity Rh_0 or to the partial or blocking antibody of Race and Wiener they are associated with the cells after brief mixture of cells and serum and are not dislodged after repeated washing of cells with saline

The inhibitor substance seems to be more stable than the corresponding Rh antibody Prolonged heating at 56 C which inactivates anti Rh agglutinins weakens the activity of the inhibitor substance but slightly and exposure to merthiolate solution over a period of time while inactivating anti Rh agglutinins appears not to affect the inhibitor substance However these measures do not raise the titer of inhibitor substance Hence the authors conclude that these procedures do not produce inhibitor substance but rather unmask its action

Presence of inhibitor substance masked by anti Rh agglutinins has been demonstrated in most of the authors anti Rh serums and it has been shown that many inactive serums have been so called because of the presence of relatively large amounts of inhibitor substance which interferes with the demonstration of anti Rh agglutinins An in vivo test has confirmed the observation that anti Rh agglutinins may be masked by inhibitor substance and that cells are capable of differential absorption of these two substances freeing agglutinins not previously demonstrable Cells of different specificity have been shown to vary in their ease of agglutination with anti Rh serums

The probable harm to the Rh positive patient from injection of serum or plasma containing anti Rh agglutinins undetected by ordinary tests because of the presence of inhibitor substance must be guarded against Similarly injection of incompatible cells into a sensitized recipient must be avoided It is now clear that neither the ordinary test tube method nor the modified compatibility test always shows the possibility of in vivo

In addition to the value of a high titer in making more tests and clearer tests possible such serums withstand necessary manipulations of adsorption with red cells or neutralization with type specific substances without serious reduction of potency This is important in producing a serum free of interfering anti A, anti B or other agglutinins High titer Rh antiserums also present interesting possibilities for production of subtype antibodies by adsorption of unwanted fractions by known suitable Rh positive erythrocytes Furthermore, choice of different Rh antigens (subtypes) for iso immunization made possible by this procedure opens up new opportunities for producing specific subtype antiserums Potent Rh antiserums should be dried from the frozen state in small quantities so that the typing material need not be held in the fluid stage for any length of time

[The next two articles especially the second are of great practical importance in connection with the direct demonstration of anti Rh agglutinins in the serum of sensitized individuals Hitherto it has been possible to detect antibodies in the serum of only about half of such persons —Eds]

Importance of Rh Inhibitor Substance in Anti Rh Serums Louis K Diamond (Harvard Univ) and Neva M Abelson[8] (Univ of Pennsylvania) report that when attempts to pool serums preparatory to their concentration by a globulin fractionation method were begun it was observed that addition of potent anti Rh serum (which agglutinates Rh_1 cells) to equally potent anti Rh_0 serum (which agglutinates Rh_1 and Rh cells) produced a mixture which inexplicably was incapable of agglutinating Rh cells Later attempts to pool serums of different anti Rh specificity before concentration led to the same unfortunate result It was therefore assumed that an inhibitor substance occurred in some serums This has since been confirmed by the authors and others

Three inactive pools were recently re examined One contained an inhibitor substance which interfered with the action of anti Rh_0 and therefore might be said to be of specificity Rh_0 In the remaining two pools inhibitor

(8) J Cl n I t g t n 24 12 126 Ja uary

easily performed at room temperature Reading is facilitated by holding the slide on a piece of ground glass placed over an ordinary electric light but a mirror or white surface will reflect sufficient natural or artificial light through the slide to reveal agglu

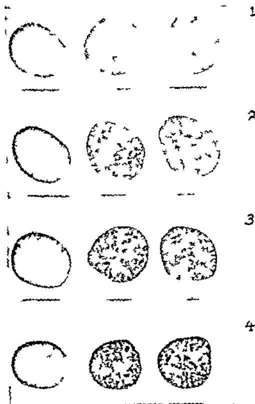


FIG 58 —F [illegible] agglutination [illegible] Rh [illegible] agglutinated Rh [illegible] blood [illegible] Rh blood [illegible] Rh blood [illegible] 2+ [illegible] 3+ [illegible] 4+ agglutination

tination from its onset When the serum is from a sensitized individual usually within one minute and certainly within three minutes plainly visible agglutination appears in one and usually in both the Rh positive bloods The Rh negative blood serves as a

agglutination Therefore before the inhibitor substance can be put to clinical trial (if indeed, it is of any therapeutic value) it is necessary not only to prepare the inhibitor serum by a method that will remove the anti Rh agglutinin leaving only the inhibitor substance, but also to devise better methods for demonstration of anti Rh agglutinins which may be masked

Demonstration of Anti Rh Agglutinins Accurate and Rapid Slide Test Louis K Diamond (Boston) and Neva M Abelson[9] (Philadelphia) state that at least two types of medical difficulties result from development of antibodies against the Rh factor in the serum of Rh negative individuals intragroup hemolytic transfusion reactions following use of Rh positive blood cells and erythroblastosis foetalis or hemolytic anemia of the newborn in offspring of sensitized women In both types laboratory demonstration of anti Rh agglutinins is desirable In tests on blood of recipients of transfusions detection of such agglutinins may anticipate the possibility of a hemolytic response or resolve the otherwise inexplicable occurrence of such a reaction Identification of anti Rh agglutinins in the blood serum of women may anticipate or substantiate development of erythroblastosis foetalis in offspring

Clinical and laboratory experience has shown that present methods of demonstrating anti Rh agglutinins in the serum of sensitized individuals are inadequate and often give misleading results The incubation test fails to show presence of anti Rh agglutinins in over 50 per cent of cases chiefly because of presence of inhibitor substances The authors present a simple and effective slide test

TECHNIC —Approximately 0 2 cc of fresh oxalated Rh negative Rh and Rh group O whole blood or washed cells is placed on an ordinary slide If washed cells are used the suspension is made up to approximately 40-50 per cent With each of these is mixed 0 1 cc of serum to be tested The mixture is gently rotated or repeatedly tilted The reaction seems to be accelerated when the slide is warmed to 37 C or thereabouts but the test is

(9) J Lab & Clin Med 30 04 21 March, 1945

CHRONOLOGIC ORDER OF PREGNANCIES OPERATIONS AND TRANSFUSIONS

C	P GN S					T N U					
	N	D t f D l v ry	D t	Statu f Ch ld	Bl d Typ f Ch ld	N	D t	D Bl d Typ	R t Fe- h l	H mo- lyt	Y Si Last S ti t
1	1	1925	3 m	S t eo ab t							
P t t A M Rh—	2	1926	8½ m	N m l	A M Rh—						
	3	1927	T m	N rm l	A M Rh+						
H b d O MN Rh+	4	1936	T m	H m lyt c d e	A MN Rh+						
		1943	Op ti			1	11/15/43	A MN Rh+	?	+	7+
2	1	19 1	T m	N rm l d d i f y	?						
P tie t A MN Rh—	2	19 2	T m	St ll mo t osity	?						
	3	1924	T m	N m l	A_2 MN Rh—						
H b d A_1 M Rh+	4	19 8	T m	H m lyt d							
	5	19 9	T rm	N m l	A MN Rh—						
	6	1934	T m	N rm l	A MN Rh—						
		1944	Op ti			1	6/2/44	O N Rh+	+	+	16
3	1	19 8	T m	N m l	A_1 MN Rh+						
	2	1929	7 m	St llb	?						
P t t A N Rh—	3	1930	T m	N m l	O MN Rh—						
	4	1931	T m	N m l	A MN Rh+						
H b d A M Rh+	5	1933	T m	N m l	A MN Rh—						
	6	1934	T rm	N m l	A MN Rh—						
	7	1938	3 m	I d d b ti	?	1	8/ 1/38	A MN Rh+	+	?	
						2	9/ 5/38	A Rh ?	—	—	
						3	9/10/38	A N Rh+	+		
						4	9/13/38	A Rh	—	—	
						5	9 16/38	A N Rh—	—	—	
	8	1941	3 m	I d dab t n	?	6	3/17/41	A M Rh+	+	?	
						7	3/18/41	A_1 M Rh+	—		
						8	3/ 1/41	O MN Rh—	—	—	
						9	3/22/41	O MN Rh—	—	—	
		1944	Op ti			10	/26/44	A_2 MN Rh+	+	+	
						11	2/ 8/44	A_1 M Rh+	+	+	
						1	3/ 1/44	A N Rh+	+	+	
						13	3/ 3 44	A_1 MN Rh—	—	—	
						14	3/ 4 44	A_1 M Rh—	—	—	
						15	3/ 6/44	A MN Rh—	—	—	

control to eliminate errors through mistaking fibrin shreds rouleaux formation or nonspecific agglutination for actual Rh agglutination (Fig 58) Rouleaux may be broken up by adding a drop of saline and stirring it into the mixture of blood and serum Fibrin is eliminated largely by using oxalated test blood but in event a drop of finger blood is used for testing, the oxalate may be added to the serum To obtain a satisfactory slide test a thick drop of blood is necessary Suspensions heavier than 50 per cent may be used but clumps are usually so close as to be hard to visualize Suspensions less than 30 per cent may show agglutination but this will vary with the type of agglutinin and its concentration in the serum For these reasons 40–50 per cent suspensions have been found most satisfactory

The authors performed more than 250 slide tests in parallel with test tube tests for anti Rh agglutinins and for inhibitor substance Ninety were on serums from mothers of erythroblastotic infants By the usual incubation technic only 37 serums were found to contain anti Rh agglutinins The slide test was positive in all these cases It was strongly positive in 38 serums known to contain anti Rh agglutinins whereas the incubation test showed varying degrees of agglutination

This method has not yet received sufficient trial to be proposed as a substitute for the incubation method Although cells of different specificity frequently react a little differently with various serums reactions are usually not clear enough on the slide for distinguishing the subgroups of Rh positive cells Moreover it is essential to determine the clinical importance of the inhibitor substance Therefore it seems necessary to continue performance of parallel tests by the three different methods

Hemolytic Transfusion Reactions Due to Rh Incompatibility Lawrence E Young and Donald H Kariher[1] (Univ of Rochester) report manifestation of sensitivity to the Rh factor in three women many years after immunization by pregnancy In one this occurred nearly 8 years and in another 16 years after the last pregnancy In the third case the latest pregnancies had been terminated by abortion so the record was somewhat confused The table shows the essential data in these cases

(1) J A M A 1 769 632 M 17 1945

for situations in which Rh incompatibility is apt to be found As an added measure of safety for Rh negative patients and in certain other cases triplicate mixtures of donor s cells and recipient s serum are checked by the test tube centrifuge technic after standing at 37 C room and refrigerator temperatures for one hour

Double Ova Pregnancy in which the Rh+ Twin Developed Erythroblastosis and died while the other remained normal is reported by Edith L Potter[2] (Univ of Chicago) The affected twin and the father were Rh+ the normal twin and the mother were Rh— It is contended that the father was heterozygous for the Rh factor and that two ova were fertilized one by a sperm carrying an Rh+ gene and the other by a sperm carrying an Rh— gene The Rh— mother had been sensitized to the Ph factor either in the previous pregnancy when an Rh+ fetus had been carried or possibly during the course of this pregnancy by the Ph+ twin Antibodies produced in the mother passed through the placentas of both fetuses but affected only the one which was Rh+ The cells of the Rh+ fetus contained the Rh antigen and could be agglutinated by Rh antibodies cells of the Rh— fetus contained no antigen and therefore could not be agglutinated The fetus whose cells were agglutinated developed erythroblastosis the one whose cells were not agglutinated remained well

Intragroup Hemolytic Transfusion Reaction in an Rh Positive Patient is reported by George Speck and Eve B Sonn[3] (New York City) It is an accepted fact that if a pregnant woman is Rh negative and if her fetus is Rh positive the baby s blood may sensitize the mother and stimulate production of Rh iso-antibodies In rare cases patients of one Rh positive type may be sensitized against blood of a different type Recent discovery of the Hr factor an antigen shared by bloods of several Rh types adds to the difficulty Just as an Rh negative individual may be sensitized against Rh positive blood

(2) J Ped t 4 449 453 Ap il, 1944
(3) Am J Ob t & Gynec 44 73 75 F bru ry 1945

These observations emphasize a number of points (1) Serious hemolytic reactions may follow transfusion without causing chills fever or other dramatic symptoms or signs (2) Sensitivity to the Rh factor once it is acquired may persist for many years, probably for life (3) Rh incompatibility is often unpredictable by any sort of in vitro matching test Prevention of such reactions consists only in always giving Rh negative blood to Rh negative patients This necessitates a complete reorganization of the blood bank so that Rh negative blood will always be available

At Strong Memorial and Rochester Municipal hospitals Rh tests are performed free on all donors and on all female patients who have received transfusion all obstetric and gynecologic patients and all male patients who have received more than two transfusions When major surgery is contemplated for such patients, blood for grouping and Rh determination is sent to the bank before 8 45 a m the day of operation Except in emergencies no female patient is sent to the operating room for major surgery unless her Rh type has been or is being determined Only Rh negative blood is given to the Rh negative patients and eventually this will be extended to include all males regardless of their history of previous transfusions Rh negative blood is also given to Rh positive infants with hemolytic disease of the newborn If Rh negative blood is not available in the bank when needed it is purchased from professional donors most of whom are members of the institutional personnel A special effort is made to keep group O, Rh negative blood in the bank at all times In emergencies if it is necessary to give this blood to persons of group AB A or B, 5 cc of a solution of A and B specific substances is added to neutralize the anti A and anti B agglutinins A transfusion requisition form similar to that recommended by Butler Danforth and Scudder and by Barton gives information regarding the obstetric history and any previous transfusion reactions This serves to keep both intern and personnel of the bank the alert

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( ) J Ped t 24 449 453 Ap il 1944
(3) Am J Obst & Gynec 44 273 75 F bru ry 1945

so may an Hr negative individual be sensitized against Hr positive blood Furthermore an Hr negative individual is always Rh positive Therefore one is not justified in feeling completely secure when transfusion is administered to an Rh positive individual

Woman 26 received a transfusion after delivery of her fourth child The blood of the donor was apparently compatible, as determined by cross matching After the patient had a severe transfusion reaction it was determined that her blood was Rh positive and Hr negative and the donor s blood was Rh negative and Hr positive The infant s blood was Rh Rh and Hr positive Wiener s hypothesis concerning this intragroup incompatibility was that the patient carri d anti Hr i o antibodies formed during her present pregnancy (or after transfusion a year previously or both) having been sensitized by Hr antigens in the infant s red blood cell Thu when she received a transfusion with Hr positive blood hemolysis occurred Anti Hr iso a glutinins could not be demonstrated in the maternal serum however this absence of iso agglutinins occurs also not infrequentl in Rh negative mothers or erythroblastotic infants The chi showed no signs of erythroblastosis the hemoglobin level never dropped below 12 Gm

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HEMOLYTIC ANEMIAS

Various types of hemolytic mechanisms are discussed in this chapter The hemolytic anemia of the new born associated with the development of anti Rh antibodies in the mother and the problem of hemolytic transfusion reactions due to Rh sensitization are discussed in the preceding chapter

The first two articles deal with the effects of trauma on red blood cells and renew interest in a subject related to certain types of hemolytic anemias —Eds

Cold Hemagglutination and Cold Hemolysis Hemolysis Produced by Shaking Cold Agglutinated Erythrocytes Daniel Stats[4] (Mount Sinai Hosp New York City) states that cold hemagglutination is the reaction of clumping that occurs when serum and red blood cells are mixed at low (below 25 C) temperatures The agglutination is caused by an antigen antibody reaction and can be completely reversed by raising the temperature above 25 C Cold hemolysis is an irreversible reaction in which hemoglobin is liberated from red blood cells at low

(4) J Cl n In t t 4 33 4 J n ar 194

temperatures Studies are presented to elucidate the relationship between these phenomena

Serums used for these tests were obtained from patients with various conditions One patient with symmetrical gangrene of the tips of his extremities and hemoglobinuria after exposure to low environmental temperatures had a titer of cold hemagglutinins of 1 30 000 for over two years Hemolytic anemia was not present A second patient had acute hemolytic anemia without hemoglobinemia the disease occurring about two weeks after onset of a primary atypical pneumonia Small doses of sulfadiazine had been administered three days before onset of anemia Improvement was rapid after blood transfusions The cold hemagglutinin titer in this case varied from 1 10 000 at the height of the disease to 1 600 during convalescence The third patient failed to respond to large doses of sulfathiazole administered for primary atypical pneumonia She was acutely ill about two weeks The cold hemagglutinin titer varied from 1 300 to 1 12 800 later falling to 1 640 during convalescence At no time was there evidence of hemolytic anemia the lowest hemoglobin level was 72 per cent A striking polymorphonuclear leukocytosis of 25 000 was an unusual feature Convalescence was prolonged but complete recovery ensued The fourth patient had severe primary atypical pneumonia After three weeks because of a hemoglobin level of 65 per cent blood transfusion was deemed advisable A blood grouping test was reported AB but none of the available donors were compatible The cold hemagglutinin titer was 1 6 400 The blood group was redetermined as group B and groups O and B donors were compatible Transfusion was not given however and recovery was uneventful There was no evidence of hemolytic anemia or hemoglobinuria The last patient had severe prolonged primary atypical pneumonia sulfonamides were not administered Early in the disease his cold hemagglutinin titer was 1 8 at the time of defervescence it was 1 5 120 This gradually diminished during convales

cence Neither hemolytic anemia nor hemoglobinuria was present

Experiments to elucidate this unusual type of hemolysis show that cold hemolysis depends jointly on a high titer (over 1 3 000) of cold hemagglutinins a high concentration of erythrocytes (over 4 per cent in the final mixture) and mechanical trauma of the cold agglutinated erythrocytes

Above a cold hemagglutinin titer of 1 3 000 there was a rough direct linear proportion between hemagglutination and hemolysis titers As the titer of cold hemagglutination fell with a rise in temperature there was concomitant decrease in the titer of cold hemolysis At 22 C, the titer of agglutinins had fallen to 1 320 and no significant hemolysis could be produced whereas at lower temperatures intense hemagglutination and hemolysis were observed

No significant hemolysis occurred when the final concentration of erythrocytes was less than 4 per cent Above this concentration there was an absolute as well as a relative increase in hemolysis coincident with increase in red blood cells This relationship was shown to be linear

Hemolysis occurred only when agglutinated cells were traumatized If a specimen was kept at 4 C for 20 minutes without tapping then transferred to a water bath at 37 C, and the tapping applied repeatedly after 1 minute at this temperature hemolysis did not result Many controls using blood from normal individuals or from patients with low titers of cold hemagglutinins yielded negative results

The fact that intense hemolysis was readily produced with heat inactivated serum old serum old lyophilyzed serum and resuspended or eluted saline solutions of cold hemagglutinins indicated that complement was not an essential agent in this hemolytic system Other confirmatory evidence of this was previously found in observations that complement was not fixed or absorbed during cold hemagglutination that hemolysis oc[illegible] at 4 C

and did not occur at 37 C and that intense hemolysis could be produced in one minute

There is no clear understanding of the role of mechanical trauma in determining the duration of life of the erythrocyte and significance of this factor in clinical hemolytic syndromes has not been studied adequately Experiments here reported indicate that under certain clearly defined conditions mechanical trauma (e g tapping of blood) of even slight degree causes liberation of large quantities of hemoglobin Direct demonstration of the importance of mechanical trauma in producing hemolysis reopens the question of participation of this factor in other types of hemolysis

Hemoglobinemia and hemolytic anemia are not invariably present in patients whose serums exhibit a high titer of cold hemagglutinins even though such serums are capable of causing cold hemolysis in vitro Even though cold hemagglutinins in high titer may be observed in rare patients with hemolytic anemia and a hemolytic mechanism may be shown it is not proved that the agglutinin is pathogenically related to the hemolytic syndrome

Paroxysmal cold hemoglobinuria may occur in patients with potent cold hemagglutinins In these patients the cold hemolysis test with tapping is positive Paroxysmal cold hemoglobinuria in syphilitics is associated with a positive Donath Landsteiner test and is different serologically from the cases with hemagglutination

Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes Shu Chu Shen W B Castle and Eleanor M Fleming[5] (Harvard Univ) present a preliminary report of a quantitative method for determining mechanical fragility of erythrocytes of some experimental factors affecting this property and of its relation to certain hemolytic anemias

METHOD —Hematocrits of samples of defibrinated blood to be compared (including a normal cont ol) were adjusted to approximately 40 per cent Seven cc of each sample was introduced into

(5) S i 100 387 389 O t 27 1944

individual cylindric 150 cc soft glass tonometers (permitting equilibration of the blood with gas mixtures), the length of the parallel portions of the sides of which was about 1 0 mm the diameter about 28 mm To each tonometer were added 50 glass beads uniformly 4 mm in diameter Tonometers were then attached at each end to clips on the periphery of two wheels approximately 150 mm in diameter These wheel were fixed at an appropriate distance apart on a horizontal axle which was rotated at 28–30 rpm usually for two hours at room temperature Before rotation an accurately measured 0 1 cc sample of blood was introduced into a test tube containing 1 cc distilled water (complete osmotic lysis) At the start and at termination of the period of rotation additional 0 1 cc samples of blood were delivered into test tubes containing 1 cc of a 1.25 per cent solution of sodium chloride (no osmotic lysis) After centrifugation, amount of hemoglobin in the supernatants in these three test tubes were determined in the Evelyn colorimeter and were designated c a and b respectively

Mechanical fragility (M F) of a sample was determined by the formula $M F = \frac{b - a}{c - a}$ and expressed as a percentage value In most instances no significant amount of cell fragmentation without release of hemoglobin resulted from the trauma as indicated by absence of hemoglobin containing cell fragments in sediments of traumatized samples as well as by unaltered osmotic resistance of cells remaining intact Accordingly percentage of hemoglobin liberated was considered equivalent to percentage of cells destroyed by trauma

When a sample of normal human blood was divided into six parts their respective M F values were 2 8 3 0 2 9 3 2 2 9 and 2 8 per cent Simultaneous determination of the M F of samples of defibrinated blood from each of six normal subjects gave the following values 3 0, 3 4 3 2, 3 4 3 2 and 2 6 per cent Percentage volume of red blood cells had a decided effect on proportion of hemoglobin liberated by trauma However because M F was expressed in terms of percentage of hemoglobin liberated rather than in absolute values differences in the mean corpuscular hemoglobin concentration of two samples could not distort the evidence as to percentages of cells destroyed Mechanical fragility increased sharply as the final spherical form was approached for washed cells suspended either in progressively hypotonic solutions of

sodium chloride or in serum progressively diluted with water In theory increased cohesion between red blood cells should increase their liability to rupture by mechanical trauma When 43 per cent by volume of washed human erythrocytes were suspended in complement inactivated serums with various titers of iso agglutinins M F of the samples remained between 3 1 and 3 7 for titers from 0 to 1 250 In experiments with bloods in which serum viscosity was greatly increased by addition of gelatin mechanical fragility of erythrocytes was not increased nor despite rouleau formation was it detectably augmented by increased serum viscosity in a case of multiple myeloma Changes in strength of the membrane of the red blood cell were found to affect mechanical fragility

Correlation between increased osmotic fragility (spheroidicity) and increased mechanical fragility was found in congenital hemolytic jaundice At splenectomy osmotic fragility of blood in the spleen exceeded that of peripheral blood After splenectomy osmotic and mechanical fragilities declined progressively and 39 days after operation both were approximately normal In patients with thermal burns and hemoglobinuria erythrocytes are relatively spheroidal and show an increase in osmotic and mechanical fragility In absence of increased osmotic fragility and cohesion between erythrocytes increases in mechanical fragility are presumably on the basis of diminished strength of cell membrane as shown in patients with pernicious anemia tested prior to treatment with liver extract M F of erythrocytes of a patient in advanced remission induced by liver extract was normal It is suggested that cohesion of erythrocytes may lead to their prompt mechanical destruction while in motion in the circulation In vitro increased mechanical destruction occurred in presence of iso-agglutinins and cold agglutinins and in experiments with sickled erythrocytes Such types of erythrocyte cohesion may cause sequestration of erythrocytes in the spleen and other

tissues, with consequent progressive increase in spheroidicity and osmotic fragility If certain red blood cells temporarily sequestered in the spleen escape before their osmotic destruction occurs, they may still be readily destroyed when resubjected to the traumatic motion of the circulation because of increased mechanical fragility

Hemolytic Anemia in Infancy J K David, Jr, and A S Minot[6] (Vanderbilt Univ) report a case of recurrent acute hemolytic anemia in an infant aged 4½ months During a hemolytic crisis it was possible to demonstrate hemolytic activity of the patient s serum against his own red blood cells and those of another patient of the same blood group After splenectomy the patient made a complete recovery and the hemolytic activity of his blood serum disappeared

During infancy recurrent hemolytic anemia, accompanied by slight icterus and enlargement of the spleen is uncommon This condition has been referred to as congenital hemolytic icterus congenital hemolytic anemia and familial spherocytosis The usual criteria by which a diagnosis is established may not all be present in the infant and the clinical course is not the one usually seen in adults Rarely is a history of similar disease in other members of the family obtained when the disease is encountered in the first year The initial manifestation often takes the form of an acute hemolytic crisis Severe anemia may develop suddenly In the infant icterus is usually slight even during the acute hemolytic crisis pallor and splenomegaly being the outstanding physical findings Because of lability of the infantile hemopoietic system changes in the peripheral blood picture are usually more striking in the infant Response of reticulocytes during a hemolytic crisis may be great, and these cells may comprise the majority of circulating erythrocytes Nucleated red blood cells are also regularly seen in the peripheral blood during the acute hemolytic crisis Increased fragility of the erythrocytes usually considered diagnostic may not be present in the infant Fu

(6) Am J Di Child 68 3 7 3 9 November 1944

dence of increased blood destruction is uniformly present There are elevation of the serum bilirubin level and increase in excretion of urobilin in the feces

Results following splenectomy are usually good Because of the rapidity with which profound anemia may develop during an acute hemolytic crisis it may be disastrous to delay splenectomy The patient should be prepared with blood transfusions After splenectomy evidence of excessive blood destruction usually disappears and the hemoglobin level and erythrocyte count gradually rise to normal

Attempts to determine the pathogenic mechanism in congenital hemolytic anemia have so far been unsuccessful Most observers have considered the abnormality to be production by the bone marrow of a defective erythrocyte the spherocyte which has increased fragility however numerous cases including the present one have been reported in which the erythrocyte fragility was normal The findings in this case are more nearly analogous to those described in certain cases of acute acquired hemolytic anemia in which hemolysins have been demonstrated The authors plan to test patients with familial hemolytic icterus for hemolytic activity demonstration of hemolysins in cases with a positive family history of the disease as well as in cases like the present one would suggest a common mechanism

Acute Hemolytic Anemia with Toxic Hepatitis Caused by Sulfadiazine Douglas Donald and Richard E Wunsch[7] (Harper Hosp Detroit) report a case

Man 47 was admitted with a diagnosis of left lower lobe pneumonia and received 2.5 Gm sodium sulfadiazine intravenously tw e at two hour intervals the first day followed by 1 Gm sulfadiazine orally at four hour intervals day and night and 10 Gm sodium bicarbonate with each dose Clinical course showed slight improvement in 48 hours but temperature remained about 101 F The third day because of low drug levels sulf diazine was increased to 1 5 Gm every four hours and 80 000 units of type V ant pneumococcic rabbit serum was given intrav nously The fourth day there was evidence of extens on to the right base and hemoglobin had dropped to 48 per cent from 92 per nt on

(7) A I t Med. 1 709 711 O t b r 1944

admission and leukocyte count was 1 ,00 the sixth day sulfadiazine was reduced to 0 5 Gm every four hours, and hemoglobin was 69 per cent and leukocyte count 19 000 The next day temperature rose to 101 F and sulfadiazine was increased to 1 5 Gm every four hours By the following morning temperature was 10, 6 F and definite icterus was present Leukocyte count rose to 30 000 hemoglobin was 71 per cent Sulfadiazine was stopped immediately In eight days 59 Gm had been given with blood levels ranging from 5 2 to 11 1 mg The ninth day hemoglobin had dropped to 5 per cent erythrocyte count was ° 666 000 and leukocyte count 25,550 It was clear that severe hemolytic anemia with toxic hepatitis had developed preceded by a sharp rise in leukocytes

The blood contained cold auto agglutinins and agglutination of donor s cells was finally controlled by incubation at ,7 C for five minutes Five transfusions of 250 cc citrated blood were given without reaction Other treatment consisted of fluids forced orally and parenterally thiamine hydrochloride 50 mg intravenously liver extract 1 cc intravenously and ferrous sulfate 1 Gm by mouth daily A high carbohydrate diet was administered The course was stormy for several days with increasing anemia but improvement began a week after transfusions were started Temperature became normal on the eighteenth hospital day The blood picture improved gradually and the patient was discharged 36 days after admission A slight anemia remained but icterus had cleared and the liver edge was no longer palpable The chest was entirely normal

[Since patients may develop cold agglutinins and hemolytic anemia without sulfonamide therapy it is not necessary to assume that there is a relationship with the drug in this patient —Eds]

Diagnosis and Treatment of Congenital Hemolytic (Spherocytic) Jaundice Report of Case with Unusual Blood Findings Altered by Liver Therapy Congenital hemolytic jaundice is a chronic blood dyscrasia generally characterized by microcytic anemia acholuric jaundice increased fragility of red blood corpuscles to hypotonic salt solution reticulocytosis splenomegaly and crises of hemolysis It has frequently been stated that patients are more jaundiced than ill The belief that the disease follows a benign course compatible with active and long life except when hemolytic crisis occurs is widely accepted Many cases however, do not follow this pattern and there is increasing tendency to emphasize the more severe aspects of the disease with ms

attitude toward therapy particularly toward blood transfusions and splenectomy

Classification of many cases is difficult Subdivision of idiopathic hemolytic jaundice into a congenital and an acquired type is not entirely satisfactory since there is no agreement on criteria used Numerous observers regard these two generally accepted types as clinical variations of the same entity

An error in diagnosis often occurs when symptoms of the disease are present particularly in children Blood *findings vary during short time intervals in the* same case making both diagnosis and classification difficult

Henry B Sutton and Norman S Moore[8] (Cornell Univ) report a case in hemolytic crisis

The blood of a man ~1 exhibited macrocytosis normal fragility and total absence of reticulocytes at initial examination A spherocytic blood picture with increased fragility and 9 5 per cent reticulocytes appeared after liver therapy Splenectomy during a crisis was followed by an immediate dramatic rise in hemoglobin and red cells and an abrupt cessation of hemolysis Transfusions were cautiously given without severe reaction but with definite signs of in rea l h mol

The authors issue a warning concerning transfusions in hemolytic jaundice and express a favorable opinion regarding emergency splenectomy

Sickle Cell Disease Observations on Behavior of Erythrocytes are reported by Robert C Murphy Jr and Shepard Shapiro[9] (St Luke's Hosp New York City) Sickle cell anemia is much more common than previously suspected and is more generally recognized The sickle cell trait occurs in at least 7 per cent of all American Negroes The ratio of symptomless sickle cell trait to clinical sickle cell disease is not definitely known but may be as high as 9 1 or 7 1 Since the trait is hereditary and dominant over the normal any one of the 900 000 odd persons with sickling in the United States may transmit the full disease It is estimated that 135 000 persons have sickle cell disease

(8) A   I c Med 1 698 708 O t be 1944
(9) A h I t Med 74 9 3 J l 1944

admission and leukocyte count was 1 500 the sixth day sulfadiazine was reduced to 0 5 Gm every four hours and hemoglobin was 69 per cent and leukocyte count 19 000 The next day temperature rose to 101 F and sulfadiazine was increased to 1 5 Gm every four hours By the following morning temperature was 103 6 F and definite icterus was present Leukocyte count rose to 30 000 hemoglobin was 71 per cent Sulfadiazine was stopped immediately In eight days 59 Gm had been given with blood levels ranging from 5 2 to 11 1 mg The ninth day hemoglobin had dropped to 53 per cent, erythrocyte count was 2 666 000 and leukocyte count 25 550 It was clear that severe hemolytic anemia with toxic hepatitis had developed, preceded by a sharp rise in leukocytes

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appears as rigid as a crystal of ice as it moves about This rigidity causes it to contrast markedly with unaltered cells which remain remarkably flexible This observation is interesting in view of the fact that sickle cells have been shown to be considerably more fragile to mechanical trauma than unaltered erythrocytes It also is important in elucidation of pathologic physiology of sickle cell disease, which depends initially on a blockade of capillaries and smaller blood vessels by abnormally shaped red corpuscles and acquires additional significance in recent observations that erythrostasis and cell trauma promote hemolysis of red cells

Sickling appears to be encouraged by coagulation of the blood specimen Erythrocytes sickle at various specific thresholds as determined by the ratio of dissociated to combined hemoglobin There is evidence to indicate that as the cells age the sickling threshold becomes lower

Sickle cells return immediately to a normal biconcave shape on exposure to oxygen Sickling appears to be unrelated to variations in electrolyte ionic balance The level of available potassium in the cell may play a significant role in sickling A single preliminary test reveals that with radioactive potassium the patient s red blood cells were about twice as permeable to potassium ion as normal control erythrocytes

Cholelithiasis in Sickle Cell Anemia Cholelithiasis is not infrequently observed in patients with sickle cell anemia H Stephen Weens[1] (Atlanta Ga) reports four cases in which gallstones were demonstrated roentgenographically A review of the literature revealed cholelithiasis in 12 of 44 cases of sickle cell anemia in which autopsy was done All 12 patients were in age groups below 40 in which according to statistics cholelithiasis is not frequent Occurrence of biliary calculi in the Negro is not rare There is however sufficient statistical evidence to indicate that cholelithiasis is encountered less frequently in Negroes than in white persons Since there is a lower incidence of cholelithiasis in the Negro

(1) A Int Med 18 191 F b ry 1945

Sickling is a property inherent in the erythrocytes and not dependent on other blood elements, although it is enhanced or inhibited by varying environmental influences Although the fundamental cause of the abnormality is to be found in a dominant gene investigation of chemical and metabolic factors may clarify the behavior of the erythrocytes in this and other blood diseases

Specimens of blood were obtained from a Negro man 21 with severe sickle cell disease, who was observed for seven months The disease was manifested by periods of violent hemolytic activity ("crises") and an intractable anemia of strictly normocytic and normochromic character Red blood cell counts hemoglobin values and hematocrit volume never rose above 70 per cent of normal and were usually much lower During one crisis such massive hemolysis occurred that 37 per cent of existing red blood cell elements were destroyed within six days High concentrations of bilirubin and urobilin in the blood reticulocytosis normoblastosis and marked roentgenographic evidence of hyperplasia of bone marrow all afforded evidence of an extreme degree of chronic hemolysis

Blood cells were studied by preparations of smears chamber counts and hanging drops and by a modification of the sealed smear technic for demonstration of sickling

The process of sickling commences with a concentration of hemoglobin in one part of the cell usually the periphery, giving it a doughnut appearance During movements of this flexible cell and also when it is stationary the cytoplasm becomes thinned at one point and eventually ruptures opening out into a crescent, sometimes having a 'ghost of cell membrane within the arc The percentage of true sickle forms is low in relation to other bizarre shapes assumed by the cells Long delicate processes and tapering points projecting from the cells always appear Sickling occurs with varying regularity and sometimes less precipitously than [illegible] The moment a cell becomes sickled it loses its f[illegible]

erative changes in the capillaries and small venules of the brain pyramidal cell degeneration glial proliferation and corpora amylacea formations No spinal cord changes were found beyond vascular congestion Hearts showed hypertrophy fatty changes albuminous degeneration edema and fragmentation of myocardial fibers in three instances vascular degeneration and perivascular cell infiltrations were present No endocardial or valvular lesions were found No changes were found in the lungs beyond marked capillary congestion Livers showed marked congestion and extensive phagocytosis of sickled erythrocytes by reticulo endothelial cells and the same findings were present in lymph nodes Spleens were enlarged in eight cases and showed marked congestion and pooling together with fibrosis of capsule trabeculae and reticular stroma Kidneys showed pronounced congestion of capillaries with glomerular thrombosis in one case Tubules showed granular degeneration pigment deposits and calcification in four cases

Clinical symptoms at onset of abdominal crises in sickle cell anemia are remarkably similar to Wintrobe's description of symptoms of rapid destruction of blood There is no evidence of extremely rapid blood destruction in these cases it is believed that symptoms are due at first to increases in the number of sickled cells and their removal from the circulation with rapidly developing shock producing terminal symptoms and death

It is suggested that the mechanism of death in these cases of abdominal crisis in sickle cell anemia is shock A possible explanation is that the anoxia accompanying anemias is increased in severity in sickle cell anemia as sickled erythrocytes do not carry or are poor carriers of oxygen to body tissues the heart in severe anemia is weakened sickled erythrocytes tend to pack or jam in small capillaries and the capillary anoxia results in plasma loss hemoconcentration and stagnation The stagnation removes available erythrocytes from the circulation increasing circulatory failure and anoxia and perpetuates the vicious cycle of shock

sickle cell anemia gains relative importance as an etiologic factor in its development in Negroes

The crises of sickle cell anemia cannot be explained solely on the basis of biliary colic However it seems possible that abdominal symptoms in some of these patients are due to cholelithiasis and associated cholecystitis Recognition of sickle cell anemia as a cause of acute and chronic abdominal symptoms is important in order that unnecessary operations may be avoided The mere presence of biliary calculi in a patient with sickle cell anemia requires careful evaluation of all clinical symptoms before operation is advised since it is commonly known that this disease increases the risk of surgical procedures

Cholelithiasis in the Negro especially in the young always demands search for presence of sickle cell anemia

Abdominal Crises in Uncomplicated Sickle Cell Anemia Wray J Tomlinson (M C A U S) presents a clinicopathologic study of 11 cases with a suggested explanation of their cause Four patients were dead on arrival at the hospital or died before they were seen by a physician Of seven patients examined during life five were in shock Clinical picture included sudden onset of distress pain rigidity or tenderness in the abdomen usually accompanied by nausea and vomiting occasional pain or tenderness in muscles and bones severe malaise chill and fever frequent jaundice early rapid peripheral vascular collapse with shock and central nervous system involvement Clinical laboratory studies revealed severe normochromic anemias (hemoglobin 11–53 per cent Sahli erythrocytes 590 000–2 400 000) and marked leukocytosis (15 000–83 600) with an absolute increase in mononuclear cells nucleated erythrocytes and sickled forms were an almost constant finding and icterus indexes were increased (10–40 units)

Postmortem examinations with special attention to changes of sickle cell anemia in a young age group with no complicating illnesses revealed congestive and degen

(7) Am J M Sc 209 7 741 Jun 1945

mation after a 10 mile hike Negro old er 32 first noted a reddish discoloration of urine five months previously after a speed march of 3 miles He had passed bloody urine several times after strenuous marching and exertion and on admission had just done so after a 15 mile hike In ne ther case was there any evidence of bone or joint abnormality and there was nothing significant in previous history or clinical findings Pyelograms in the first case revealed that both kidneys had a bifid pelvis The only significant laboratory find ngs besides hemoglobinemia and hemoglobinuria were leukocytosis and change in albumin globulin ratio in the first patient Hemoglob nemia was definite in both cases giving weight to the theory that a general intravascular hemolysis occurs instead of hemolysis l m ted only to renal blood vessels There was no evidence of increased erythrocyte fragility in these patients

Appearance of hemoglobinuria following marching simplifies the diagnosis but several other conditions must be excluded (1) paroxysmal hemoglobinuria after cold exposure (2) paroxysmal nocturnal hemoglobinuria (Marchiafava Micheli syndrome) (3) paralytic myoglobinuria or Haff disease (4) favism a form of allergic paroxysmal hemoglobinuria (5) blackwater fever (6) hemoglobinuria due to poisons (7) hemoglobinuria associated with Clostridium welchii infections of wounds (8) bartonella infections (Oroya fever) (9) acute acquired hemolytic anemia (Lederer s type)

PERNICIOUS AND RELATED MACPOCYTIC ANEMIAS

Attention is directed to the last three articles in this section because of the descr ption therein of macrocytic anemias which fail to respond to usual dosage of efined liver extracts given parenterally but which respond either to crude liver extract administered orally or to larg amounts of relatively crude liver extracts given parenterally Such anem as are ipso facto not due to so called extrins c factor defic ency as was first pointed out for certain tropical macro ytic anemias by Wills Napier and others

The following arti le by Farrar and Hyman is a useful summary of the present therapy of pernicious anemia with most of which we heartily agree —Eds

Pernicious Anemia Clinical aspects are reviewed by George E Farrar Jr and Harold L Hyman[4] (Temple

(4) M Cl n N rth Am 9 9 50 J ry 1945

Further examination of cases of abdominal crisis and other conditions in sickle cell anemia should be directed toward determining the presence of shock If shock is present, use of blood and plasma may greatly alter the clinical picture Blood of donors showing the sickling trait must not be transfused in these cases

March Hemoglobinuria Robert E Hobbs[3] (M C A U S) reports two cases March hemoglobinuria is a syndrome characterized by hemoglobinemia and hemoglobinuria following marching or running It was first described by Fleischer in 1881 and is quite rare According to Gilligan and Blumgart, only 40 cases had been described to 1941 most of these by German authors In 29 cases hemoglobinuria followed walking or marching and in 11 it occurred in athletes after long runs

Accompanying symptoms are usually trivial, in most reported cases there were none Symptoms most commonly reported are vague pains in abdomen, back and/or thighs Jaundice does not occur because the total amount of blood hemolyzed during an attack is small and attacks are usually infrequent In one reported case, liver and spleen were enlarged liver enlargement was reported in two other cases Etiology is unknown it has been postulated that it is probably a strange perversion of a normal physiologic process accompanying muscular activity

Lordosis is frequently present in affected individuals and Witts believes that it produces a local circulatory disturbance in the kidney with intravascular destruction of erythrocytes in kidney vessels, followed by hemoglobinuria He stated that only a small quantity of the liberated hemoglobin passes into the general circulation the major part being excreted as promptly as produced Conversely Gilligan and Blumgart found a plasma hemoglobin level of 210 mg per 100 cc in one patient and stated that only about 10 per cent of the liberated hemoglobin is excreted in the urine

White soldier, 20 first noted bloody urine 17 days before exam

(3) Am. J Clin Path 14 485 488 September 1944

Significant physical signs when present are lemon yellow pallor a clean tongue which may be either very red with a smooth swollen shiny tip and lateral portions or pale shrunken smooth and shiny all over impaired sense of position and vibration and a positive Romberg sign and retinal pallor with flame shaped retinal hemorrhages Other less significant and less frequent findings are a dilated heart and a soft systolic murmur hepatomegaly splenomegaly [rare today —Eds] dependent edema and diminished or hyperactive deep tendon reflexes

Important laboratory findings are macrocytic anemia—mean corpuscular volume greater than 97 cubic microns or a mean red cell diameter greater than 7 5 microns with cells smaller and larger than those of normal blood (color index is usually greater than 1) achlorhydria gastrica—no free acid in four samples of gastric juice aspirated at intervals of 15 minutes after hypodermic injection of 0 5 mg histamine base Other findings are increase of nucleated red cells including more than 2 per cent megaloblasts in films prepared from a few drops of fluid aspirated from sternal bone marrow leukopenia with relative lymphocytosis hypersegmentation of nuclei of neutrophils and moderate decrease in platelets and increase in concentration of serum bilirubin which gives an indirect van den Bergh reaction Some experience is required in proper interpretation of marrow films Sternal aspiration is indicated in those patients in whom liver therapy fails in all cases with unusual clinical features and in cases of severe anemia which are neither macrocytic nor hypochromic

The following program has proved satisfactory in treatment of uncomplicated cases in the initial or recurrent stage of relapse 15 units of liver extract U S P intramuscularly (upper outer quadrant of buttock) daily for three days and then weekly until the erythrocyte count reaches 4 500 000–5 000 000 (usually about seven weekly doses) For maintenance therapy a dose of 15

Univ) Clinical recognition of primary (addisonian) pernicious anemia is facilitated by neurologic and gastro-intestinal symptoms frequently present Chronic and mild anemias of iron deficiency type (hypochromic and microcytic) are often not recognized until blood examination demonstrates a low hemoglobin level Symptoms of chronic anemia per se such as weakness fatigue dyspnea and palpitation on slight exertion, dizziness with exertion or change of posture and mild swelling of the ankles by the end of the day occur in other common clinical conditions Pallor is often insufficient to demand attention and may be masked by cosmetics In macrocytic anemias the frequently associated stomatitis interferes with recognition of mucous membrane pallor and the slight icterus of skin and scleras is confusing especially in artificial light Conversely pale patients often have essentially normal blood counts

Minot presented a clarifying analysis of symptomatology of pernicious anemia based on 100 cases The cases were divided into four types according to symptoms (1) gastro intestinal including sore mouth anorexia epigastric fulness after meals constipation nausea diarrhea and dyspepsia suggesting peptic ulcer or biliary tract disease (2) neurologic including numbness and tingling of feet and hands difficulty in walking stumbling in the dark urinary incontinence headache and psychic disturbances (3) generalized or anemic including fatigue, weakness dyspnea palpitation vertigo and usually marked pallor and (4) cardiac including angina pectoris dyspnea palpitation edema of ankles weakness and usually marked pallor Minot noted that symptoms had been present an average of 2 19 and 1 28 years in groups 1 and 2 respectively before pernicious anemia was suspected In contrast pernicious anemia was diagnosed in less than one year in anemic and cardiac clinical types In general medical worl Minot s emphasis on paresthesias, sore tongue and indigestion is helpful in recognition of pernicious anemia

weekly until the erythrocyte count reaches 4 500 000 followed by injections of 30 units every week or two until a satisfactory or apparently maximal (after one to two years) symptomatic relief of neurologic manifestations is achieved A permanent maintenance dose at the rate of 2–3 units daily is indicated Intramuscular administration of thiamine hydrochloride in doses of about 10 mg three times weekly should also be carried out during the first two or three months [There is no convincing evidence that this is necessary or useful —Eds] Use of less concentrated liver extracts is favored by some physicians but the large volume of extract necessary to provide the required number of units of antianemic material makes their sole use both uncomfortable and impractical Satisfactory results are obtainable with highly concentrated liver extracts Brewers yeast powder in doses of 30–60 Gm daily by mouth or ingestion of ½ lb liver several times a week will supply plentiful amounts of all factors in the vitamin B complex [But is unnecessary if a well balanced diet is taken —Eds]

Among the macrocytic anemias one of the more common is that of pregnancy It is characterized by an erythrocyte count of less than 3 500 000 a color index greater than 1 1 and a mean corpuscular volume greater than 97 allowance being made for the physiologic increase in plasma volume which reaches a maximum of about 25 per cent at the sixth month of gestation As in other macrocytic anemias variation in size of erythrocytes is less pronounced than in primary pernicious anemia Leukopenia and paresthesias are unusual A general dietary deficiency is usually found and liver extract therapy alone is not rapidly and completely effective A diet containing 50 Gm or more protein daily in the form of meat eggs milk and cheese is necessary [No desirable but not necessary Some patients do however require orally administered crude liver extracts for a response — Eds]

Extensive reactions of the small intestine especially when a blind loop of bowel is present may be followed

units every four weeks usually proves to be adequate

Severe untoward reactions to intramuscular injections of liver extract are infrequent Local pain and tenderness flushing of the upper part of the body and faintness are the most common complaints Less often fever and local induration, persisting for days occur Injections should be continued as these reactions usually cease after a few weeks An anaphylactic type of reaction is rare however, erythema, urticaria, tachycardia hypotension, angioneurotic edema and asthma can be terrifying A hypodermic injection of 0 5 cc of 1 1 000 epinephrine hydrochloride solution should be immediately available whenever liver is injected Allergic reactions are more likely to occur after a period of neglected treatment or in patients receiving injections at intervals of two or more weeks Small doses (0 125 cc) repeated every 30–60 minutes will avoid serious reactions. These patients may tolerate small doses three times a week, but reactions often recur as soon as the interval between doses is lengthened Changing to extract marketed by another manufacturer may not avoid the untoward symptoms Some evidence suggests that the sensitivity is to some ingredient used in all liver extracts rather than to the animal species of liver Many commercially available extracts are derived from a mixture of pig and cow livers An extract prepared from horse liver is available and may be useful in some patients. Oral liver extract may be tried but sensitivity reactions may follow ingestion also Oral use of dried defatted gastric mucosa of the pig (ventriculin N N R) in doses of 10 Gm four times daily (or once daily as a maintenance dose) or brewers yeast powder in doses of 30–60 Gm daily may solve this therapeutic problem [The last is impractical —Eds.]

The patient with pernicious anemia and moderate or marked evidence of degeneration of the posterior and lateral columns of the spinal cord requires more intensive and persistent therapy The following program is adequate and practical 200 units of liver extract U S P intramuscularly during the first week [illegible] ts

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Severe untoward reactions to intramuscular injections of liver extract are infrequent Local pain and tenderness flushing of the upper part of the body and faintness are the most common complaints Less often fever and local induration persisting for days occur Injections should be continued as these reactions usually cease after a few weeks An anaphylactic type of reaction is rare however erythema urticaria tachycardia hypotension angioneurotic edema and asthma can be terrifying A hypodermic injection of 0 5 cc of 1 1 000 epinephrine hydrochloride solution should be immediately available whenever liver is injected Allergic reactions are more likely to occur after a period of neglected treatment or in patients receiving injections at intervals of two or more weeks Small doses (0 125 cc) repeated every 30–60 minutes will avoid serious reactions. These patients may tolerate small doses three times a week, but reactions often recur as soon as the interval between doses is lengthened. Changing to extract marketed by another manufacturer may not avoid the untoward symptoms. Some evidence suggests that the sensitivity is to some ingredient used in all liver extracts rather than to the animal species of liver Many commercially available extracts are derived from a mixture of pig and cow livers An extract prepared from horse liver is available and may be useful in some patients Oral liver extract may be tried but sensitivity reactions may follow ingestion also Oral use of dried defatted gastric mucosa of the pig (ventriculin N.N R) in doses of 10 Gm four times daily (or once daily as a maintenance dose) or brewers yeast powder in doses of 30–60 Gm. daily may solve this therapeutic problem. [The last is impractical —Eds.]

The patient with pernicious anemia and moderate or marked evidence of degeneration of the posterior and lateral columns of the spinal cord requires more intensive and persistent therapy The following program is adequate and practical 200 units of liver extract U S P intramuscularly during the first week

Pernicious Anemia and Carcinoma of Stomach Autopsy studies concerning the interrelationship of these diseases are presented by Henry S Kaplan and Leo G Rigler (Univ of Minnesota) Data from the literature suggest that pernicious anemia and carcinoma of the stomach probably occur frequently in the same individual It is doubtful that gastric carcinoma is a direct precursor of pernicious anemia There is almost no evidence to establish or refute the possibility that pernicious anemia may be only one perhaps a very minor one among several causes of carcinoma of the stomach A final possibility is that a factor common to both conditions may be a precursor of both or a concomitant of one and a precursor of the other Among factors enumerated are gastritis achlorhydria and achylia constitutional and hereditary factors and liver therapy for pernicious anemia

In 23 231 autopsies on individuals over 45 years 293 cases of pernicious anemia were found Thirty six of the 293 patients also had carcinoma of the stomach an incidence of 12 3 per cent which is over three times as great as the incidence in the remaining autopsy population of the same age Unequivocally these statistics indicate that there is an etiologic relationship between pernicious anemia and carcinoma of the stomach Patients with pernicious anemia should therefore be examined frequently to detect onset of carcinoma of the stomach

[Our experience does not indicate any unusual inciden e of gastric or other carc noma at least in pat ents with pernic ous anemia in ma ntained remission Many pat ents w th advanced carcinoma of the stomach exhib t some anemia from blood loss metastase to bone marrow or other causes Such an mias may be misdiagnosed as pernic ous anemia unless subjected to rigorous cl nical study The authors series began in 1915 but it was not until 1926 that the essential criterion of therapeutic response to liver extract ould hav been employed Nevertheless the autho s conclusio seem probabl —Eds]

Progressive Addisonian Pernicious Anemia Successfully Treated with Intravenous Choline Chloride Sudden failure of an occasional patient with Addison

(5) Am J M S 09 339 348 M h 194

by severe macrocytic anemia and usually other manifestations of nutritional deficiency The anemia usually responds to parenteral liver therapy, but much larger doses are necessary than in pernicious anemia (about 50 units weekly) Resection of the blind loop may relieve the macrocytic anemia

Extrinsic factor deficiency unassociated with other manifestations of nutritional deficiency, is rare The important therapeutic measure is provision of an adequate diet especially of the extrinsic factor such as 2 oz or more of brewers yeast powder or autolyzed yeast (vegex) daily The powder is best administered in a milkshake vegex may be mixed with cheese and eaten in a sandwich. [Best treatment is precisely that for pernicious anemia, but some of these rare patients have other associated dietary defects —Eds]

Mild degrees of macrocytosis associated with slight depressions of hemoglobin and erythrocytes are frequent in acute hepatitis and more chronic cirrhotic disorders Some of the increase in size of erythrocytes may be related to the decreased osmotic pressure of hypoproteinemic blood plasma commonly present [Not so, because the osmotic pressure of the electrolytes completely overshadows the effect of any protein deficiency In this respect contrast erythrocytes with capillaries —Eds] An actual deficiency in the liver antianemia factor may exist Liver extract 10–20 units three times weekly parenterally, is valuable in general management of patients with liver disease [but rarely has any demonstrable hemopoietic effects —Eds]

Pellagra is usually associated with a hypochromic anemia Liver extract has long been of recognized value in treatment of pellagra and is superior [theoretically —Eds] to nicotinamide alone in that liver provides all the factors of the vitamin B complex [In practice in severe cases of pellagra liver extract may not supply enough nicotinic acid to control a serious situation It contains very little thiamine —Eds]

bone marrow or both is present particularly when a pro gressive anemia develops during administration of ade quate purified liver extract in the absence of factors known to interfere with a therapeutic response

[We are inclined to await confirmation of the authors conclu sions by others before accepting them In the first place patient with severe fully developed pernicious anemia who have exhibited a clinical response to liver extract therapy and who have subse quently relapsed during regular and usually adequate therapy with liver extract parenterally are extremely rare In our ex perience such an event indicates the advent of some other recog nizable and distinct d sease process or complicat on In the second place in patients with nutrit onal macrocyt anemia which might eas ly be confused with pernicious anemia such as are described in later articles in this chapter we have found choline hydro chloride completely ineffectual —Eds]

Eosinophilia Following Parenteral Liver Therapy Harold A Hanno and Maurice Mensh[7] (Philadelphia) review the literature and report a case of pronounced eosinophilia (19 850 leukocytes 11 286 eosinophils) in a previously splenectomized woman 45 who had received a daily intramuscular injection of crude liver extract for about six weeks for a condition thought to be nonob structive biliary cirrhosis The eosinophil count declined after liver extract was discontinued

An allergic mechanism has been hypothesized by many as an explanation of eosinophil response to liver In none of the reports reviewed was any mention made of con comitant findings suggestive or indicative of a clinical allergic state On the other hand numerous reports have appeared of allergic manifestations occurring in the course of parenteral liver extract therapy and in only one was mention made of eosinophilia Since allergic re actions to liver taken orally are extremely uncommon as compared with those following parenteral liver therapy and since eosinophilia following whole liver by mouth is much more frequent and much more pronounced than that following liver extract given parenterally the au thors conclude that eosinophilia following administra tion of liver or liver extract is not related to development of allergy in any of its known manifestations In their

(7) Am J M S 09 57 579 M 1945

Biermer s disease (addisonian pernicious anemia) to respond to adequate amounts of purified liver extracts in the absence of factors known to interfere with a therapeutic response has been observed by F B Moosnick E M Schleicher and W E Peterson[6] (Minneapolis Gen l Hosp) in the last few years and has also been noted by others Little is known of the chemical nature of the liver factor (anti-pernicious anemia factor) or the physiologic dose or about development of a progressive anemic state under adequate amounts of purified liver extracts the authors believe their observation may indicate one of the mechanisms responsible for the sudden refractory behavior of certain patients

Man 61 had for several years responded characteristically to administration of crude liver extracts and maintained a normal peripheral blood status but a progressive anemic state developed when purified liver extracts were substituted He became increasingly sensitive to liver extracts of all types and all attempts at desensitization failed The anemic state responded well to choline chloride (Merck) 5 per cent solution, 20 ml intravenously for 16 days Biopsy of liver and bone marrow tissue showed marked fatty metamorphosis of both organs which was believed to have been the reason for failure to maintain a normal blood status

The fact that a remission of the anemic state, reduction of mean corpuscular diameter of erythrocytes and return of bone marrow toward normal histology and volume occurred on choline therapy only seems to indicate that an adequate amount of hemopoietin (anti-pernicious anemia factor) was stored in the liver but not effectively elaborated because of the fatty state It is assumed that purified liver extracts contain either no choline or amounts too small to be effective with respect to fat transportation and deposition in certain individuals

Amount of choline and period of administration essential for re establishment of a physiologic state of liver and bone marrow and elaboration of hemopoietin in man require further investigation It is suggested that choline chloride (Merck) or substances containing choline may be supplemented when fatty metamorphosis of liver or

(6) J Clin. In estigat on 4 278 8 M y 1945

tongue but tongue changes are not as constant as in addisonian anemia Slight edema is common and massive edema sometimes occurs Patients have generally been described as showing a yellowish pallor but in Callender s series this was exceptional even with profound anemia A delicate pearly white appearance was far more characteristic

Splenic enlargement of varying degree is present in about 30 per cent of cases Less frequently the liver also is enlarged Gradual diminution accompanies clinical improvement Purpuric eruptions or hemorrhages from mucous membranes are occasionally seen Retinal hemorrhages have been found in nearly half the patients examined ophthalmoscopically Although pyrexia is common association with sepsis has generally been reported as infrequent However in the author s series and that of Davidson Davis and Innes septic complications occurred in 26 of the combined series of 41 patients Pre eclamptic toxemia and ante and postpartum hemorrhage may occur

The blood picture is remarkably variable Earlier reports described a severe macrocytic hyperchromic anemia indistinguishable from Addison s anemia but in recent series including the author s less characteristic findings are reported Hemoglobin level is frequently below 30 or even 20 per cent by the time diagnosis is made Although the color index is usually normal or raised it may be below unity and sometimes as low as 0 75 Mean corpuscular volume is usually high but may be normal Mean cell diameter (Price Jones s method) has ranged from 6 89 to 8 98 microns In most cases it is within normal limits Fragility of red cells may be increased normal or diminished In blood films the cells may appear normal in size and shape with uniform staining At the other extreme anisocytosis and poikilocytosis are obvious features ovalocytosis has also been noted Extensive search often reveals nucleated red cells of both normoblastic and megaloblastic series in peripheral blood films Typically they are fully hemoglobinized

case there were no clinical manifestations of frank allergy and the intradermal skin test with the liver extract used was negative

There is a question whether absence of the spleen may have played a role in development of eosinophilia since there is some evidence that there is a relationship between the spleen and the number of eosinophils in the circulating blood Instances of eosinophilia following splenectomy have been reported

Critical Review of Pernicious Anemia of Pregnancy is presented by Sheila T E Callender[8] (Oxford) with a report of 25 cases Many earlier records of this condition are of limited value because hematologic data are often scanty or vague and in some instances an alternative diagnosis of iron deficiency anemia posthemorrhagic anemia or anemia due to infection cannot be excluded Some 205 previously reported cases may be accepted as probable instances of pernicious anemia of pregnancy, though diagnosis was proved in less than half Two particular features were regarded by Callender as diagnostic true megaloblasts in the peripheral blood and megaloblastic change in the bone marrow

Pernicious anemia of pregnancy occurs at any age during the child bearing period in both primi and multigravidas Although most patients are poor and have a defective diet a few exceptions have been noted A previous history of anemia or ill health is not unduly frequent and a family history of anemia has been recorded only three times Usually symptoms arise during the third trimester or in the puerperium but occasionally they date from early pregnancy or miscarriage Rapidity of onset may be striking or so insidious that the condition is not recognized until many months after confinement

Apart from general symptoms common to all severe anemias there may be marked gastro intestinal complaints Excessive vomiting or diarrhea is a feature in 40–50 per cent Patients may also complain of sore

(8) Quart J Med 13 5 105 Apr July 1944

given and treatment continued until a satisfactory response has occurred or preferably until the blood count is normal In refractory cases careful attention should be paid to any foci of sepsis especially urinary infection and transfusions should be given to maintain a good blood level until the liver takes effect

[*Important* If remission to parenterally administered liver extract does not immediately take place large amounts of crude *liver extract or whole liver should be administered orally* The last three articles in this section bear directly on this matter — Eds]

Nutritional Macrocytic Anemia in Patients with Pellagra or Deficiency of Vitamin B Complex is described with a review of 56 cases by Carl V Moore R Vilter V Minnich and T D Spies[9] The patients had existed

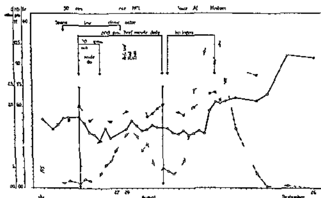


FIG 59

for years on diets inadequate in animal protein and vitamins of the B complex most of them also had clinical evidence of pellagra ariboflavinosis or beriberi In 25 red blood cell count ranged from 1 000 000 to 3 000 000 Males predominated in a ratio of 3 1 and most patients were over 50 The most striking clinical manifestations were weakness pallor glossitis and intermittent or persistent diarrhea The skin either showed pellagrous dermatitis or was rough hyperpigmented and dry Splen

(9) J L b & Clin M d 29 1226 1255 D mbe 1944

Ehrlich megaloblasts, but occasionally more basophilic forms are found Nucleated red cells in mitosis may also be seen A low reticulocyte count is usual for untreated patients but sometimes it is high White cell counts range from 1 000 to 12 000, with occasional higher values up to 45 000 A pathologic leukocytosis is only rarely found Conversely true leukopenia is common, granular cells being principally affected In blood films a few myelocytes and young forms are nearly always present, and occasionally macropolycytes and hypersegmented forms characteristic of Addison s anemia are seen

Some reports indicate a slight rise in plasma bilirubin but this was not seen in Callender's series Achlorhydria is not the rule Among 121 records of gastric analyses only 34 women had complete achlorhydria and some of these may not have been histamine fast

Marrow changes before treatment are similar to those in Addison s anemia In most cases there is a mixed megaloblastic and normoblastic reaction with formation of characteristic clumps of deeply basophilic promegaloblasts and megaloblasts Multinuclear megaloblasts and giant forms are not uncommon and degenerate cells with a coarse reticulate and sometimes irregularly lobed nucleus may be seen Leukopoiesis is sometimes strikingly predominant the leuko erythrogenic ratio being more than 3 1 Pathologic white cells showing vacuoles peculiar invaginations of nuclei and discrepancy between nuclear and cytoplasmic development are also found many being giant forms No particularly characteristic changes in megakaryocytes have been observed In most cases typical megaloblasts are easily found but occasionally there are only a few and careful search for them is necessary The response of bone marrow changes to treatment is identical with that in true pernicious anemia The megaloblastic character disappears rapidly and there is striking proliferation of macronormoblasts and normoblasts Evidence of abnormal leukopoiesis seems to persist longer than megaloblastic erythropoiesis

In treatment adequate doses of liver

two exceptions serum iron values were low or normal rather than high and (5) each of 25 subjects to whom a source of extrinsic factor was given showed a reticulocyte response and usually a red blood cell increase Since confusion of nutritional macrocytic anemia with pernicious anemia is likely unless free gastric acid is present or response to extrinsic factor is demonstrated it is possible in regions where deficiencies of vitamin B complex are endemic that nutritional macrocytic anemia is not infrequently diagnosed as pernicious anemia Some cases reported as pernicious anemia with normal gastric acidity may actually be cases of nutritional macrocytic anemia This has practical importance in that extrinsic factor deficiencies can be corrected by diet alone and do not require life long administration of liver extract

Differentiation of this form of nutritional macrocytic anemia from sprue may actually not be justifiable Macrocytic anemia of sprue is apparently caused by poor intake of extrinsic factor poor absorption of erythrocyte maturation factor inadequate production of intrinsic factor or a combination of these influences Its pathogenesis therefore may be similar to that described for nutritional macrocytic anemia The final answer as to whether the two conditions represent two distinct entities or are identical may have to wait until their etiology is more completely understood Comparison of the syndrome described with nutritional macrocytic anemia of the tropics is difficult because (1) clinical descriptions of the latter disease are not uniform and (2) confusion exists regarding the response they show to parenteral injection of purified liver extracts Nutritional macrocytic anemia in the tropics is apparently more common among women and is frequently associated with pregnancy There are other clinical differences which may be fundamental but also may be produced largely by differences in dietary habits and in types of infections and parasitic diseases to which patients are exposed Final decision as to the possible etiologic identity of these two anemias must await availability of pure extrinsic factor

omegaly was found only in those patients who had had malaria Eighteen showed signs of mild peripheral neuritis but combined system disease was not observed Physical or laboratory evidences of increased hemolysis were absent Peripheral blood and bone marrow were cytologically indistinguishable from those of addisonian pernicious anemia Free hydrochloric acid was found in the gastric contents of 16 patients at the time they were first studied in 5 others free acid was found on subsequent examinations

All subjects showed prompt therapeutic response to parenteral injection of highly purified liver extracts They also showed an increase in reticulocytes when fed beef muscle an 80 per cent alcoholic extract of beef muscle or crude liver extract When oral administration was prolonged red blood cells increased Figure 59 shows the submaximal hematologic response produced by daily administration of 200 Gm beef muscle to a patient, 50 with nutritional macrocytic anemia Subsequent therapy with a highly purified liver extract injected intramuscularly caused a striking secondary reticulocyte response and rapid rise in red blood cell count During a second period of study two years later evidence suggested that absorption from the intestinal tract was impaired

Studies of pathogenesis of the anemia indicate that it is probably caused by a dietary deficiency of extrinsic factor associated in many but not all instances with poor absorption from the intestinal tract Inadequate production of intrinsic factor is probably also a contributing influence Thiamine niacin riboflavin, calcium pantothenate pyridoxine inositol para aminobenzoic acid and choline given together both orally and parenterally did not affect the erythropoietic equilibrium

The chief points of difference between this form of anemia and addisonian pernicious anemia were (1) 22 of 25 subjects had free hydrochloric acid in gastric secretions at least part of the time (2) evidence indicated that they also produced intrinsic factor (3) icteric indexes were uniformly within normal limits (4) with

gested that arrested megaloblastic maturation in these refractory anemias results from a deficiency of some additional hemopoietic factor present in proteolyzed liver but absent or quantitatively inadequate in fractionated liver extracts

Proteolyzed Liver in Treatment of Refractory Anemias L J Davis and L S P Davidson (Univ of Edinburgh) report on the response to proteolyzed liver administered orally in 13 cases of severe anemia which had proved refractory to treatment with injections of

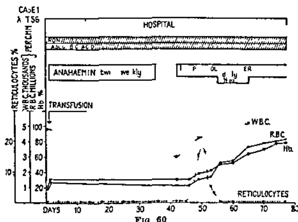


Fig 60

liver extracts of known potency In five cases morphology of the peripheral blood and sternal marrow was respectively macrocytic and megaloblastic and was typical of addisonian pernicious anemia although only one case conformed fully in other respects to the usual diagnostic criteria for this disease In all these cases administration of proteolyzed liver resulted in a prompt and vigorous hemopoietic response and rapid restoration of the patient to normal health The first patient was an elderly woman who presented no features incompatible with a diagnosis of classic addisonian pernicious anemia apart from failure to respond to liver extract The evidence in

(2) Q rt J Med 13 53 73 Ap July 1944

Macrocytic Anemia in Children L J Davis[1] (Univ of Edinburgh) states that anemias characterized by a macrocytic peripheral blood picture may be divided into two main groups, according to whether the marrow is megaloblastic or normoblastic In severe untreated megaloblastic anemias the marrow picture is easily recognizable However in mild cases especially if iron deficiency also exists and in cases in which liver therapy has recently been instituted, careful study may be required

Rapid replacement of megaloblastic by normoblastic bone marrow and subsequent restoration of a normal blood picture usually follow treatment of megaloblastic macrocytic anemia by injections of fractionated liver extracts containing the hemopoietic principle effective in pernicious anemia Occasional cases, however are permanently or temporarily refractory to liver extract therapy

Review of previous reports of macrocytic anemias in childhood emphasizes rarity of the condition and inadequacy of data for justification of a diagnosis of addisonian pernicious anemia in most cases

In two of Davis three cases in children aged 12 13 and 15 circumstantial evidence pointed to long standing nutritional dysfunction but there was no adequate evidence for diagnosis of any clinical entity of likely etiologic significance In Case 2 hypochromic anemia had been present about a year before onset of hyperchromic anemia In Case 3 etiology was obscure and failure in hemopoiesis apparently was temporary Although the blood and sternal marrow pictures were typical of pernicious anemia various clinical features rendered such a diagnosis improbable It was believed that defective assimilation from the alimentary tract may have been the paramount factor

In Case 1 exceedingly large injections of liver extract were required the other two patients were completely unresponsive to parenteral liver therapy but were readily amenable to proteolyzed liver given by mouth It is sug

(1) Ar h D Childhood 19 147 154 D mber 1944

majority of megaloblastic anemias is due to a deficiency of the liver principle of Castle present in fractionated liver extracts in refractory megaloblastic anemias it results from an additional deficiency consequent on failure in production or absorption of some other unknown factor which is present in adequate amount and assimilable form in proteolyzed liver and presumably also in whole liver According to this view the therapeutic effect of the unknown factor in refractory megaloblastic anemias is contingent on an adequate quantity of antianemic principle of Castle It is believed that proteolyzed liver is of peculiar value as a convenient means of supplying both factors

The authors emphasize that they do not advocate proteolyzed liver for routine treatment of addisonian pernicious anemia since in uncomplicated cases injections of potent liver extract are highly effective and provide the most economical means of administration Proteolyzed liver should be reserved for cases refractory to parenteral treatment

Nutritional Macrocytic Anemia Response to Substance Other Than Anti-Pernicious Anemia Principle Janet Watson and W B Castle[3] (Boston) made observations on three female patients with nutritional macrocytic anemia The first and third became anemic during pregnancy All gave histories of striking dietary inadequacy showed free hydrochloric acid in the gastric contents and had macrocytic and slightly hypochromic anemia with moderate leukopenia and thrombocytopenia Anisocytosis and poikilocytosis of red blood cells were less pronounced than in comparable cases of pernicious anemia Differential white counts were normal There were no neural manifestations

Hematologic data apparently demonstrated that prompt response to orally administered liver extracts immediately followed therapeutic failure of liver extracts given parenterally even in multiple U S P units daily In Cases 1 and 2 response to liver extract given orally

(3) P S E p B l & M 1 8 84 86 1 34

this case (Fig 60) that proteolyzed liver succeeded where parenteral liver extracts failed is clear and conclusive

In three other cases the anemia was also macrocytic but the sternal marrow films showed "dimorphic" erythropoiesis Proteolyzed liver in these cases was followed by only partial blood regeneration with survival of the patients in moderate health The remaining five cases were of the aplastic type with hypocellular normoblastic sternal marrow and completely failed to respond to proteolyzed liver or any other form of treatment

The authors refute the argument that recoveries in the cases of megaloblastic anemia were due to cumulative effect of antecedent injections of liver extract with the proteolyzed liver and that effect of the latter was no more than would have occurred if injections of liver extract had been continued by the fact that response to proteolyzed liver was invariably immediate and vigorous

There are two possible explanations for apparent superiority of proteolyzed liver in treatment of refractory megaloblastic anemias (1) It is conceivable that these refractory anemias differ from classic pernicious anemia only in requiring a relatively greater quantity of hemopoietic principle and that greater quantities of the hemopoietic substance were assimilated from proteolyzed liver This view is difficult to accept since it has been shown repeatedly that the active hemopoietic principle of liver is 60–100 times as effective when given by injection as by mouth. Moreover dosage of liver extract in these cases was considerably greater than that necessary to produce a satisfactory response in pernicious anemia (2) The more likely explanation is that proteolyzed liver contains some factor of hemopoietic value lacking or present only in inadequate quantities in fractionated liver extracts Since proteolyzed liver probably contains in a predigested form all constituents of raw liver except fat it is reasonable to assume that it has the same therapeutic properties

The authors suggest as a provisional hypothesis that while failure of maturation of megaloblasts in the great

(Univ of Arkansas) Oral administration of three doses daily of choline chloride (10 mg per kg each) to five dogs produced reductions of 30–43 per cent in their red blood cell counts Milder anemias were produced in two other animals Anemias so produced are hyperchromic and probably the result of a depression of erythropoiesis Reticulocyte percentages during the anemia varied from about 0 05 to 0 6 per cent

Intramuscular injection of adequate doses of purified solutions of liver to three anemic dogs caused an increase of erythrocytes which was pronounced by the seventh day and (in two animals) approximated normal after four weeks These responses occurred despite continued choline administration Reticulocyte percentages arose to only 1 5–2 3 in these dogs during liver therapy Peak reticulocytosis occurred on the sixth day of therapy

Stomach U S P fed in daily doses of 20 Gm to a mildly anemic dog caused a return of the red cell count and hemoglobin percentage to normal within 12 days despite continued choline feeding

Oral administration of atropine sulfate three times daily to an anemic dog caused the red cell count to return to normal in four weeks despite continued choline feeding

Davis suggests the possibility that dogs with choline induced anemia could be used for biologic assay of antipernicious anemia preparations

[The anemia producing effect of choline described here has not been found to occur in normal men by Wintrobe or in a patient with macrocytic anemia of cirrhosis by us —Eds]

HYPOCHROMIC ANEMIAS

Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs was determined by Carl V Moore Reubenia Dubach Virginia Minnich and Harold K Roberts[5] in an attempt to resolve the conflict of views of clinicians and of laboratory workers using dogs It is generally agreed that in patients with

(5) J Clin Investigation 3 755 767 September 1944

occurred after intramuscular administration of more refined preparations of known effectiveness in pernicious anemia failed to produce results demonstrating a deficiency of some substance other than the principle effective in pernicious anemia In Case 3, a special preparation of Liver Extract Lilly produced results only when it was given orally in 10 times the amount that was ineffective on intramuscular injection, suggesting that the tenfold increase in dosage was the cause of therapeutic success and eliminating as an explanation of failure following parenteral administration a difference in chemical properties of the preparation used However, the fact that in pernicious anemia an aqueous solution of Liver Extract Lilly has been found 60 times as active hemopoietically when injected as when given orally suggests an alternative explanation Possibly the digestive organs in this type of patient form a new hemopoietic substance from liver extract in a fashion analogous to the food-gastric factor relationship in addisonian pernicious anemia

As was first pointed out for tropical macrocytic anemias in such exceptional patients as here reported the basic nutritional deficiency differs from that in patients with addisonian pernicious anemia Consequently the 'unitarian' hypothesis concerning the etiology of pernicious and other nutritional macrocytic anemias suggested by Strauss and Castle does not apply to these particular patients This distinction emphasizes the desirability of a therapeutic trial of orally administered liver extract in macrocytic anemias particularly those of pregnancy when they are refractory to parenterally administered liver extracts

[Subsequent studies indicate that although refractory to multiple U S P units of refined parenteral liver extract such patients will respond to cruder liver extracts given parenterally provided enough of the material is administered —Ed]

Experimental Production of a Hyperchromic Anemia in Dogs Which Is Responsive to Anti-Pernicious Anemia Treatment is described by John Emerson Davis[4]

(4) Am J Physiol. 14? 40 -408 October 1944

complete on the fourth day but this sample affords an estimate of rate of utilization The isotope level in red cells was usually taken as the average found on the sixth and eighth days The second feeding was always given immediately after the eighth day sample was taken and the level as determined by the sample served as baseline for determination of additional uptake due to this feeding Similarly the third feeding was given the eighth day following the second feeding

In the nine patients with hypochromic anemia to whom iron tagged with radioactive isotope was administered *it appeared that the ferrous iron salt is much more readily* absorbed and subsequently utilized than the corresponding ferric salt or ferric ammonium citrate fed under the same conditions

Eleven experiments on standardized dogs showed that utilization of ferrous iron was much greater than that of the corresponding ferric salt There was no difference in response to iron reduced to the ferrous form by addition of cevitamic acid as contrasted with that treated with sulfur dioxide

In patients individual response to a given dose of tagged iron is so variable that it is not feasible to study the relative utilization of different iron preparations in different subjects Studies must be controlled in the same individuals to eliminate this source of error

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OTHER ANEMIAS

Hematologic and Genetic Study of Transmission of Thalassemia (Cooley's Anemia Mediterranean Anemia) is presented by William N Valentine and James V Neel[7] (Univ of Rochester)

Thalassemia is a rare but well known fatal disease characterized by a chronic progressive hypochromic and microcytic type of anemia peripheral erythroblastosis increased number of target and oval red blood cells decreased fragility of erythrocytes splenomegaly depo

(7) Arch Int Med 74 185 196 September 1944

hypochromic anemia soluble ferrous salts containing only one fourth to one sixth the amount of iron present in soluble ferric salts have comparable therapeutic effect Workers with anemic dogs find no such differences Accordingly comparison was made in the same 'normal' and iron deficient human subjects and in the same 'normal' and iron deficient dogs of the degree to which comparable test doses of ferrous and ferric radioactive iron were assimilated The quantity of iron varied from 1 to 4 mg iron per kg body weight administration was under fasting conditions The amount of radioactive iron which subsequently appeared as hemoglobin in the peripheral blood was used as measure of the amount absorbed Human subjects absorbed 1½ to 15 times more ferrous than ferric iron while dogs either absorbed both valence forms to a comparable degree or showed preferential assimilation of ferrous salts Because species of animals have been shown to differ in this respect discussion of the valence form in which iron is most readily absorbed from the intestinal tract should be related to the species under consideration

Relative Absorption and Utilization of Ferrous and Ferric Iron in Anemia As Determined with the Radioactive Isotope P F Hahn Edgar Jones I C Lowe C R Meneely and Wendell Peacock[6] report a study on nine human subjects

When radioactive iron is found in the red blood cell of peripheral blood it is indisputably the material fed In quantitating results it must be assumed that all or nearly all absorbed iron is used in construction of new hemoglobin and is not stored to any great extent Under conditions of iron deficiency there are nearly complete utilization and minimal storage

In nearly every instance use of ferrous and ferric salts was alternated to control the experiments and to obtain the sharpest possible contrast of results Following the first feeding, blood samples were taken on the fourth sixth and eighth days Utilization is usually in

(6) Am J Phy 1 147 191 197 F) y 194

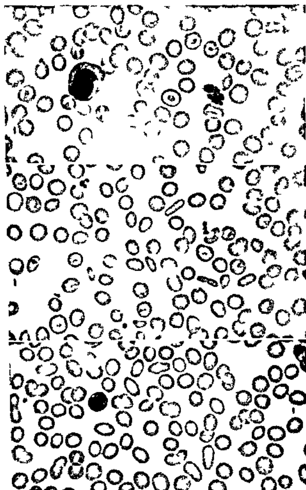


FIG 6 (t p) —Bl od me f F Y um s t rg t ll
FIG 63 (t) —Bl d m f M M n m us t get a d l ll
FI 64 (bottom) —Bl d m f m mb f n th f m ly m ld l
vt

sition of pigment in the viscera and changes in the bones The condition was early noted to have a familial incidence and to be virtually restricted to Mediterranean peoples In some instances erythrocytes of apparently healthy parents and of siblings of patients with this anemia showed decreased fragility Wintrobe and coworkers, in 1940 described occurrence in several Italian families of a relatively mild anemia which did not respond to iron therapy resembling thalassemia in many

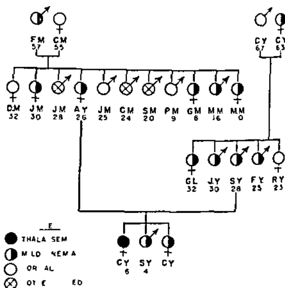


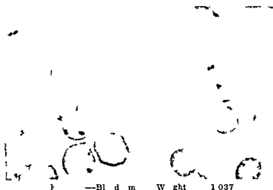
Fig 61 —Pedigree of family Y and collateral

respects but quantitatively much less severe Erythrocytes were characteristically hypochromic and microcytic ovalocytes and target cells were present but no peripheral erythroblastosis was observed There was a tendency toward splenomegaly and hyperplasia of the bone marrow Fragility of erythrocytes was reduced Wintrobe also showed that the blood picture in parents of children with thalassemia was abnormal and identical with the mild anemia he had previously described

tionally inferior and more susceptible to infections of all sorts Their detection and diagnosis are a new medical responsibility

Certain cases of familial ovalocytosis in Mediterranean peoples may be instances of thalassemia minor

Anemia Associated with Unidentified Erythrocytic Inclusions after Splenectomy Alwin M Pappenheimer William I Thompson Donald D Parker and Katharine Edsall Smith[8] (Columbia Univ) observed three cases of anemia two ending fatally in which red blood cells contained iron reacting intracorpuscular structures the



F —Bl d m W ght 1 037

nature of which has not been determined (Fig 65) They appeared only after splenectomy The two patients who died presented progressive febrile anemia with an undamaged hyperactive marrow unable effectively to arrest the anemia Both had splenomegaly and neither benefited by splenectomy Treatment with liver extract and iron was ineffective and transfusion reactions were severe both before and after splenectomy The third case although somewhat similar clinically and hematologically is much less severe and does not seem to be rapidly progressing to a fatal termination

The inclusions were present in a fairly large proportion of erythrocytes With Wright s stain they appeared

(8) Q t J M d 14 1 (Ap l 1945

The authors collected hematologic data and pedigrees for families of three patients with thalassemia and one with the similar but milder anemia first described by Wintrobe (Fig 61) These four families included 34 persons Twenty four had hematologic findings qualitatively similar but quantitatively less severe than those of full blown thalassemia including increased resistance of erythrocytes to hypotonic solutions of sodium chloride target and oval red blood cells microcytosis and hypochromia (Figs 62 64)

Three theories have been advanced concerning the possible genetic mechanisms involved in the familial incidence of thalassemia (1) The disease is due to homozygosity for a factor which when heterozygous produces the mild anemia i e the factor is either an incomplete recessive or a semidominant character (2) The severe and the mild condition have the same genetic basis and are due to a dominant factor variably expressed as determined by environmental and genetic modifiers In one person heterozygous for this factor extreme thalassemia may develop whereas in another heterozygote there may be only slight changes (3) Simultaneous presence of two nonallelomorphic dominant factors one inherited from each parent causes the disease The bulk of the statistical evidence favors the hypothesis that the mild state is due to heterozygosity for a factor which when homozygous results in full blown thalassemia Consequently it is suggested on the basis of pathologic and genetic evidence that the full blown disease be designated thalassemia major and the milder carrier state thalassemia minor

Discovery of carriers of thalassemia adds a previously undetected morbid condition to adult medicine and takes thalassemia in a broad sense out of the purely pediatric field Many carriers present syndromes which may mimic other diseased states—rheumatic fever lead poisoning hemolytic jaundice and the splenomegalies [and particularly iron deficiency anemia —Eds] Others while presenting less definite symptoms undoubtedly ... ttu

occasional occurrence of anemia in hemochromatosis Butt and Wilder describing 30 patients with a diagnosis of hemochromatosis made during life found an average of 3 990 000 red blood cells with slight macrocytosis in 3 Wintrobe and Shumacker found pigmentary cirrhosis with macrocytic anemia in one personal case and four from the literature Pernicious anemia associated with hemochromatosis was reported by Poth and by Cain Kracke mentioned a patient with macrocytic anemia hepatomegaly and splenomegaly without glycosuria and without abnormal pigmentation of the skin in whom visceral changes of hemochromatosis were found at autopsy [We have observed a similar case —Eds] In Meader s case immature forms of erythrocytes and granulocytes were present in the peripheral blood Thus it is apparent that anemia is not a feature of hemochromatosis and if it is present that it is due to complicating conditions

Aplastic anemia associated with hemochromatosis has been reported by Kark and by Mackey Bomford and Rhoads reported three cases making with the present case six such instances Except for one patient who lived above a garage and complained of the odor of fumes none gave a history of exposure to potentially toxic substances Kark and Mackey attributed development of hemochromatosis to inability of the body to utilize or excrete iron introduced in the form of hemoglobin Mackey believed that the amount of iron recovered from his patient s liver was directly related to the amount of hemoglobin administered in transfusions Bomford and Rhoads did not commit themselves regarding relationship of hemochromatosis to transfusions and stated that two of their patients had not received an exceptional number of transfusions In the authors case, the liver contained 29 Gm iron During the entire illness the patient received 12 8 L blood making only about 6 5 Gm iron introduced into the body by this means and leaving an excess of 22 5 Gm

In four of the five reported cases changes in bone mar

as minute coccoid or slightly elongated structures, assuming mostly a dark reddish purple or purplish blue color although sometimes a bluish component was distinguished Staining in Giemsa's solution was identical Rod forms were occasionally found but were far less numerous than coccoid bodies The number of bodies in a single erythrocyte varied from 1 to 20 or more They were never found within leukocytes Many affected erythrocytes seemed to be depleted of hemoglobin save for a narrow rim at the periphery The bodies were often concentrated at the cell margins

When these bodies were first observed it seemed likely that they were parasites However detailed study made it inadvisable to classify them under any existing genera of nonprotozoal blood parasites There is a general morphologic resemblance to bartonella haemobartonella and perhaps also eperythrozoon but differential features are sufficient to exclude them from each of these genera A second possibility is that the bodies are not parasitic but represent an iron containing component (not hemosiderin) derived from breakdown of hemoglobin or a precursor of hemoglobin related to the so called siderocytes described by Gruneberg and Case in animals Whether the bodies in these cases are identical with these siderophil granules is difficult to decide should they be so interpreted their appearance in large numbers in the peripheral blood in certain cases of anemia is still of great interest and demands further investigation

Aplastic Anemia and Its Association with Hemochromatosis Kurt Zeltmacher and Margaret Bevans[9] (New York Univ) state that although hemochromatosis is a comparatively rare condition it is associated with aplastic anemia frequently enough to suggest that the association is more than accidental

Sheldon stated that the blood picture is normal except for a slight degree of anemia which is by no means constant, and is no more than is to be expected in the terminal stages of any chronic disease ' Naegeli mentioned

(9) A h I t Med 75 395 407 Jun 1945

lownward despite repeated transfus ons and death occurr 1 three months after admission

Autopsy showed iron pigmentation of skin lymph nodes ad renal glands kidneys heart muscle lungs and thyroid and pr tate glands There was also fibrosis and pigmentation of liver a 1 pancreas Anatomic diagnoses included pseudo aplast anemia f unknown origin mild extramedullary hemopoiesis hemochroma tos s portal cirrhosis hepatosplenomegaly coronary sclerosi cardiac hypertrophy and dilatation myocardial fibro is pulmo nary emphysema and fibrosi pyel ti cy tien edema of the right lower extrem ty and nodular hyperplas a of the thyroid gland

Idiopathic Congenital (and Probably Familial) Methemoglobinemia Ashton Graybiel J L Lilienthal Jr and Richard L Riley[1] (M C U S N R) report a case

Youth first seen at age 19 had been blue at bi th and re ma ned so During infancy and early childhood he wa in poor health Act v ties were lim te l by fat gue and shortness of breath and scho l attendanc was irregular At 1 he left school an l did l ght work without compla nt Diet generally had been ade quate and include l citrus fru ts an l other foods containing relatively large amount of ascorbic ac d. He had never taken drugs known to cause yanos s or p gmentation A cousin had al been blue at birth and remained so until death at 14

Physical examination showed malnutrition and cyanosis Ears tongue l ps and espec ally gingival margins showed intens vanosis Nail beds were blu but there was no clubbing of fin gers or toes Scleral v ssels were abnormally prominent a d dark blue Retinal arter es and veins appeared almost black Respira t ons and heart rhythm and s ze were normal A sl ght vstol murmur was heard over the base Blood pressure was 1 0/100

Blood examination revealed no abnormality n num ber o morphology of leukocytes e ythrocyte count was 5 800 000 an l hemoglob n 16 Gm Roentgen examinat on of heart and lung disclosed no abnormalities except slight right vent icular hype trophy and the aorti knob placed higher than usual Electro card ogram was normal except for right ax s dev ation ndex plus 19 and angle plus 117 d grees X rays of long bo e reveal 1 normal ep physeal de elopment

A ample of arterial blood obta ned for gas analysis wa chocolate colored Oxyhemoglob n content was 13 volume per cent oxyhemoglob n capac ty of the same sample was only 15 volume per cent an l the brown color rema ned unchanged after equilibration w th air The hemoglobin concentration of 16 Gm corresponds to an oxyhemoglobin capacity of 1 volun e pe ent The con lus on was ne capable that a la g amount of some abno mal pigment wa present Methemoglobin content

(1) B ll J h H pki H p 6 155 16 Ap l 194

row were described as pseudo aplastic simular chan es were observed in the present case The cause of aplst i anemia is obscure but its relationship to exogenous and endogenous toxins is assumed Such toxic elements pos sibly in connection with deficiency factors may produce permanent liver damage Thus patients with prolonged pseudo aplastic anemia come to have retention of iron pigmentation and cirrhosis of the liver as the pancreas becomes involved diabetes develops Iron derived from destruction of intrinsic and of transfused blood is not used in formation of hemoglobin but is mechanically de posited in various organs If the aplastic anemia is of sufficient duration large quantities of iron accumulate Increased iron in the presence of hepatic cirrhosis produces a picture indistinguishable from that of hemochromatosis In contrast to idiopathic hemochromatosis increased hemolysis is active in production of hemochromatosis associated with pseudo aplastic anemia

Man (5 was hospitalize l for complaints of weaknes dy pnea and swelling of the legs He had be n hospitalize l first 10 months before and had been readmitte l five times for bloo l transfusions. Since appearance of con estive h art failure five months before he had been receiving maintenance doses of digitalis and mer curial diuretics At the la t admission there were 1 400 000 erythrocytes 4 000 leuk cyte and 216 000 platelets hemoglobin con tent was 36 per cent and reticulocytes 3 1 per cent Mean cor puscular volume was 100 cubic microns and mean corpuscular hemoglobin 33 mi romicrograms mean corpuscular hemo lobin content was 3" per cent Color index was 1 1 Re l cells showed marked aniso yto is and poikilocytosi Many macrocytes were een Polychromatophilic and large ba ophili stippled red cells were rare Two normol lasts in 100 white blood cells were coun ed During l ospitalization the red cell count vari l between 1 1 0 000 and 000 000 hemoglobin between 34 and 54 p r cent and leu kocyte count between 2 00 and 6 100 Reticulocyte count d creased to below 1 per cent during the last two month Smears f bone marrow were very cellular There was an increa ed per c ntag of n l ate l re l cells with basophilic and polychromatic normoblasts predominating Mature granulocytes were markedly diminishe l Hemosiderin wa present in reticulum cell , which were also increa e l

The patient received 1. 8 L blood in 1" tran fusions There was hypergly emia but no glyco uria The c a stea l ly

that this occurs within the erythrocyte Site of the metabolic defect which permits production of methemoglobin is unknown

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POLYCYTHEMIA VERA

Radioactive Phosphorus in Treatment of Polycythemia Vera Results and Hematologic Complications Byron E Hall Charles H Watkins Malcolm M Hargraves and Herbert Z Giffin[2] (Mayo Clinic) discuss the course in seven men and five women aged 41–73 The initial dose of radioactive phosphorus administered intravenously usually was 4–7 mc and second or third injections were given during ensuing weeks Since it was not available regularly treatment in some cases was inadequate Eleven patients had had the disease 6 months to 13 years and had received various other treatment Diagnosis in the other patient was made two weeks before administration of radioactive phosphorus 1 500 cc blood was withdrawn in two weeks Blood examinations were made at one month intervals On recurrence of polycythemia additional radioactive phosphorus was administered when available The period of observation after treatment ranged from 5 to 26 months

Remission was satisfactory in eight cases and incomplete in two Results in the two others were unsatisfactory but treatment was believed to be inadequate Both clinical and hematologic improvement occurred in the patients who had satisfactory remissions with complete relief of symptoms attributable to polycythemia Remissions lasted 8–26 months six lasted over 1 year Doses required to induce satisfactory remissions varied considerably In a woman 41 who had had mild polycythemia for five years remission of 16 months followed a single injection of only 4 mc radioactive phosphorus In another instance definite improvement was produced by administration of 5 mc Conversely the patient who obtained a remission of 26 months received three injec

(2) Am J M S 209 71 717 J 1945

determined by two methods, was 8 1 Gm and 8 5 Gm ...o signifi cant quantities of sulfhemoglobin were present Methemo lobin level remained practically unchanged when the blood was kept at room temperature for 24 hours in contrast methemo lobin in blood of patients with toxic methemoglobinemia is largely reduced to normal hemoglobin under the same conditions This alone was fairly conclusive evidence of familial idiopathic met hemoglobinemia

After 19 days treatment with 100 mg ascorbic acid and 0 6 Gm sodium bicarbonate three times daily by mouth methemoglobin concentration had fallen to 1 7 Gm, and normal hemoglobin had increased from 13 1 to 15 8 Gm Following treatment he became somewhat irritable and was not always co operative Psychologic tests before and after treatment showed no im provement No change in rate of dark adaptation was detected. Cardiovascular system revealed great reduction in intensity of cyanosis Otherwise findings were essentially the same as before treatment except that the electrocardiogram no lonwer showed right axis deviation Exercise tolerance was determined by the step test Shortly before treatment the score was 28 indicating poor fitness for hard work. Two months later the score was 5 a low average score the increase of 85 per cent representing marked improvement

Most patients with methemoglobinemia from birth have been considered initially to have congenital heart disease Absence of marked structural changes in the heart disproportion between relatively good exercise tol erance and intense cyanosis and absence of clubbin are important features in differential diagnosis Met hemoglobinemia may be suspected in patients with in tense cyanosis whose blood is chocolate colored and fails to become crimson on exposure to air Presence of met hemoglobin can be established by spectroscopic examina tion It is likely that some patients showing cyanosis now regarded as having congenital heart disease have idiopathic methemoglobinemia

The exact mechanism of effect of ascorbic acid is un known it seems reasonable to assume that ascorbic acid in increased concentration in the blood acts as a non specific biologic reducing agent rather than as a supple ment to any primary deficiency of ascorbic acid Ascorbic acid reduces methemoglobin to normally functioning hemoglobin and speed of the reaction in v

those reported I y Hempelmann and hi a ociates (this YEAR BOOK page 404) therapy with radioactive phosphorus is not without its disadvantages and complications —Eds]

MONONUCLEOSIS AND OTHER LEUKOCYTIC RESPONSES TO INFECTIONS

In this chapter are di cussed conditions with leukocytoses of certain characte t type presumably n response to specific nonpyogenic infect ons —Eds.

Infectious Mononucleosis Joseph H Press Edmund L Shlevin and Albert I I osen[3] (Jewish Hosp Brooklyn) studied 96 cases in 10 years Despite many theories etiology remains obscure Children and young adults are usually affected The condition is rare in persons over 40 However c ses in infants of 7 months and adults of 70 have been reported In the authors series 83 patients were between 1 and 0 30 of these were aged 21-25 There were 54 males and 42 females all white Only one instance in a Negro has been reported There was no evidence of an occupational factor Seasonal distribution of cases was spring 33 winter 25 summer 22 fall 16 No autopsy material was available

Tidy classified this disease into three types (1) The glandular or Pfeiffer s type occurs especially in children lymph node enlargement is the predominant sign (2) The angiose type (monocytic angina) has often been confused clinically with diphtheria After a prodromal period of one to three weeks marked by increasing pyrexia and malaise the throat becomes sore and a diphtheric membrane forms on or near the tonsils and may persist many days (3) The febrile type the commonest type in adults is of sudden onset with fever headache and malaise A macular or papular rash may then appear and spots often develop in crops The lymph nodes may not become enlarged until two or three weeks after onset The fever is not characteristic is usually irregular and persists for one to three weeks Although this classification covers most cases it frequently proves inadequate because of protean manifestations

(3) A I t M d 4[?] 6 Ap 1 1945

tions during two months, totaling 13 mc A fourth injection of 2 68 mc was given 16 months after the third although polycythemia had not recurred

No toxic reactions developed and radiation sickness did not occur However hematologic complications including anemia leukopenia and thrombocytopenia were noted in several cases and acute leukemia in one Anemia observed in five cases was of hypochromic or normochromic, normocytic type In one case it developed months after the last injection and in the other four occurred 7 to 25 months afterward in all it was mild and relatively transient Leukopenia was present in five cases, but in only two was the leukocyte count less than 4 000 in one it dropped to 2 200 and in the other to 3 600 two and three weeks after administration of radioactive phosphorus Leukopenia was of short duration in all cases and no serious complications resulted Thrombocytopenia occurred in four cases platelet counts varying from 29 000 to 86 000 Petechiae developed on the lower extremities in two patients and disappeared in a few weeks as the platelet counts gradually rose A man 63 who had had polycythemia 3½ years died with the blood picture of acute leukopenic myelogenous leukemia after a remission of 13 months Polycythemia vera may terminate with the clinical and hematologic picture of chronic myelogenous leukemia but development of acute terminal leukemia is unusual Theoretically the possibility of a causal relationship between administration of radioactive phosphorus and occurrence of acute leukemia should be considered but such a relationship seems unlikely for two reasons (1) the first definite signs of leukemia developed long after the material had lost its radioactivity except for an infinitesimal quantity and (2) signs of leukemia did not appear in other patients receiving treatment over longer periods

[Polycythemia vera is of course treated in a most logical and physiologic way by repeated bleeding (see 1944 Year Book of General Medicine page 37_) Except for convenience radioactive phosphorus presumably has no advantage over suitable x ray therapy As indicated by the above results as]

and differential count usually begin to return to normal

Most authorities believe that the specific cells respon sible for the distinctive features of the peripheral blood smear belong to the lymphocyte series Gall concluded that they are atypical but relatively mature lymphocytes Size varies from that of a small lymphocyte to that of a monocyte Cytoplasm is typically deeply baso philic but may be light it may be vacuolated giving the cell a foamy appearance Azurophilic granules are com mon The nucleus may be round oval or indented and may occupy part of or almost the entire cell It may be centrally or eccentrically placed and characteristically stains deeply the chromatin appearing in clumps Oc casionally fenestrations are present These cells were present in 74 cases

Erythrocyte count remained essentially unaltered Only one patient exhibited a paucity of platelets with an associated bleeding tendency this being a known case of long standing idiopathic thrombocytopenic purpura No abnormalities in the blood picture were observed in four patients One observed from early stages through the entire course presented splenomegaly with a strongly positive Paul Bunnell reaction The second patient was seen after two weeks of illness with lymphadenopathy and a positive heterophil antibody reaction The third seen after three weeks presented lymphadenopathy splenomegaly and a positive heterophil antibody reac tion The fourth seen the tenth week of illness presented splenomegaly with a definite Paul Bunnell reaction

Sixty four patients of the 90 on whom the Paul Bunnell test was performed had sheep cell agglutinin titers of 1 128 or more In two cases titers were 1 8 000 Titer was not related to severity of the disease or degree of lymphocytosis Although this test has great diagnostic value in the presence of a characteristic clinical and hematologic picture a negative Paul Bunnell reaction does not preclude infectious mononucleosis In 59 of the 64 patients with positive Paul Bunnell reaction it was positive during the first four weeks

Incubation periods of 1–28 days have been reported The most nearly correct figure is about 11 days Onset may be sudden or gradual Symptoms may be mild or severe with pronounced prostration Most frequent complaints in the authors' series were fever (98 per cent) headache (35 4 per cent) malaise (34 3 per cent), sore throat (31 2 per cent) and chills or chilly sensations (28 1 per cent) Sixty six patients presented throat involvement only 30 had subjective complaints of sore throat Lymph node enlargement was present in 76 cases. Frequency of involvement of groups of lymph nodes was cervical 72 axillary 28 inguinal, 28 epitrochlear 9 mediastinal 3 Thirty seven patients had involvement of two or more groups of nodes The spleen was palpably enlarged in 69 patients Of the remaining 27 20 demonstrated definite lymphadenopathy Splenic enlargement without apparent lymphadenopathy was observed in 13 patients Absence of both splenomegaly and apparent lymph node enlargement was noted in seven Twenty six patients had hepatomegaly, all but two with associated splenomegaly Skin lesions were present in 18 7 per cent and jaundice in 5 2 per cent

Leukopenia was observed in 38 patients during the first week The lowest white cell count was 2 200 In practically all these patients the total count returned to normal or above in the second week of illness Of 58 patients without leukopenia during the first week practically all had leukocytosis However the highest leukocyte counts were usually recorded during the second week Most patients had counts varying between 10 000 and 20 000 only 10 had counts above 20 000 Lymphocytosis is the most constant feature 80 patients had lymphocytosis most marked during the second week but practically all presented a lesser degree during the first week Roughly increase in lymphocytes paralleled the degree of leukocytosis However lymphocytosis was present even in most cases with leukopenia at onset Lymphocytes constituted 40–90 per cent of white cells usually 60–80 per cent Toward the end of the third week, le

rule it out In this series 75 per cent of the patients had positive reactions

The sheep cell agglutination test becomes positive usually between the sixth and the twenty first day of illness and ordinarily remains so for two to four months after onset although it may return to negative much sooner or not until much later Usually a positive test is found for a longer period if the reaction was at some time positive in high dilution If only one diagnostic venipuncture is done it should be performed not earlier than the ninth nor later than the thirtieth day preferably between the twelfth and the twenty first

The test has considerable value especially in febrile illnesses in which diagnosis is uncertain It should be performed in cases of fever of unknown origin acute throat infections when diagnosis is not clear acute or subacute lymphadenopathy local or generalized unexplained leukocytosis or leukopenia with relative lymphocytosis or monocytosis whether illness is present or not illness diagnosed as leukemia and in definite or suspected cases of infectious mononucleosis When infectious mononucleosis is suspected the test should be repeated if the titer rises or if the test becomes positive after having been negative diagnosis is established provided there has been no injection of horse serum

Spontaneous Splenic Rupture in Infectious Mononucleosis Ward Darley William C Black Charles Smith and Frederick A Good (Univ of Colorado) report a case of this rare complication

Man had been n good healtl unt l persistent fe er de (l oped after a mild sor throat Symptom p ogressed and two weeks later i fect ous mononucleosis was d agnosed A few day late jaundice abd m nal te derness and fever were reced n, but he was awaken d by a stabbing agonizing pa n in mi l epigast um and l a k and went nto sh ck General condit or improved following administ at on of blood plasma and glucos solution n normal saline Lapa otomy 14 hours after the attack showed the abdom nal cavity filled with blood mak ng inspection of viscera mpo bl Palpation rev aled a large tear near the hilus of the pleen and the spleen was removed Convalescence

(5) Am J M S 08 381 384 S pt b 1944

Acute leukemia is foremost in differential diagnosis. Absence of red cell changes, normal platelet count and absence of immature leukocytes are against a diagnosis of leukemia. Other conditions that sometimes cause confusion are granulocytopenia, diphtheria, Vincent's angina, Hodgkin's disease, tonsillitis, scarlet fever, typhoid fever, malaria, tuberculous adenitis, undulant fever and central nervous system infections. However, hematologic and serologic studies should establish the diagnosis.

Heterophil Antibody Reaction in Infectious Mononucleosis. Robert E Kaufman[4] (M C, A U S) describes changes in Davidsohn's technic of performing the sheep cell agglutination test and reports 83 cases of infectious mononucleosis.

TECHNIC.—The serum is inactivated for 4 minutes at 61 C instead of for 30 minutes at 56 C. Results of agglutination instead of being read after two hours' incubation at room temperature and again after overnight in the icebox, are read after centrifugation at high speed for five minutes and thorough shaking with the fingers. Five minutes instead of one hour is sufficient for absorbing serums if tubes are shaken thoroughly during that time. This applies to both guinea pig kidney and beef erythrocytes. Results are reported merely as positive or negative. All results are read macroscopically, because after centrifugation there is not enough diagnostic difference to warrant use of the microscope.

Tests were performed in 78 of 83 proved cases of infectious mononucleosis. Clinical, hematologic and serologic aspects are important in diagnosis; if any two are definite the diagnosis is established. No cases in this series which were positive clinically and serologically had consistently negative blood smears. However, in many clinically and hematologically positive cases the serologic findings were negative, and in a few hematologically and serologically positive cases the clinical manifestations were slight or extremely atypical.

Agglutination in a dilution of 1:28 with the correct differential absorption tests is considered a positive reaction. A positive reaction supports the diagnosis of infectious mononucleosis, but a negative reaction does not

(4) Ann Int Med 21 30 1 August 1944

eosinophilia appeared as the total count began to drop In a few this occurred during the highest count and persisted for seven months

The characteristic picture of the predominating small lymphocytes is normal except for relatively few smudge or degenerated cells in the stained smear and the uniformly negative reaction to the Paul Bunnell test in dilutions over 1 32

The authors believe that this condition is due to an infectious agent, but efforts to demonstrate a bacterial or virus cause were fruitless

In no patient was tuberculosis appreciably made worse by the lymphocytosis several showed within three months an increased rate of improvement as indicated by roentgenograms of the chest and some did not Two patients who had previously had enlarged spleens showed a decrease in the size of the palpable spleen and an increased rate of clinical improvement within three months

Tropical Eosinophilia Frimodt Moller and Barton in 1940 described a clinical condition characterized by leukocytosis and eosinophilia and associated with cough fever loss of weight and strength blood stained sputum or frank hemoptysis and asthma or bronchitis in varying combinations or degrees The roentgen picture of the chest closely resembled that of miliary tuberculosis The common pattern of signs and symptoms the distinctive blood picture absence of any laboratory evidence of tuberculosis and the uniformly good prognosis justified considering this condition a new syndrome An allergic origin was suggested chiefly because of the eosinophilia Subsequently several additional reports have appeared

I G K Menon[7] (Pasteur Inst of Southern India Coonoor) presents data on eight cases observed within a year The condition is more common below age 30 and particularly between ages 20 and 30 The usual sequence is an initial attack of fever (99–102 F) persisting some days or several weeks (at about 100 F) transient lung changes more persistent cough and more slowly

(7) I d M G 80 24 40 J n ry 1945

was satisfactory and he was discharged 12 days after operation Blood count one month later showed hemoglobin 84 per cent red cells 3 820 000 leukocytes 11,100, with 45 per cent neutrophils 43 per cent lymphocytes, 6 per cent large mononuclear cells 6 per cent eosinophils

Pathologic examination of the spleen showed a ragged tear along the anterior margin 4 cm long with protruding soft red pulp This opening through the capsule extended obliquely across the convex surface 2 cm and was 2 5 cm deep Its margins were hemorrhagic and surfaces made by cutting in the region showed several solid masses of red blood clot embedded in the splenic substance No evidence of direct cause of the fracture or hemorrhage was obtained Possibly a local lesion previously existed at the site of initial hemorrhage if so it had been obliterated Microscopic examination showed increase in lymphoid elements and an atypical cell similar to that of infectious mononucleosis found in peripheral blood

Infectious Lymphocytosis Daniel Leo Finucane and Rowland S Philips[6] report an epidemic of 21 cases in the children s wards of Glenn Dale Md Sanatorium during the winter of 1942 43

In differential diagnosis the three most important diseases are infectious mononucleosis lymphatic leukemia and pertussis Pronounced total lymphocytosis is found in children with pertussis or lymphatic leukemia moderate lymphocytosis in children with infectious mononucleosis and only slight total or relative lymphocytosis in those with tuberculosis and postinfectious conditions In infectious lymphocytosis there is marked total leukocytosis with high relative lymphocytosis and no clinical signs or symptoms

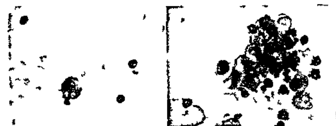
The children were aged $1\frac{1}{2}$–$5\frac{1}{2}$ years Leukocyte counts ranged from 22 500 to 120 000 with a relative lymphocytosis of 62–97 per cent In most cases total counts were over 40 000 in three they were over 100 000 In all but four percentage of lymphocytes was 85 or over, and in these four it was 62 plus In no case was there any symptom at onset, the condition being discovered by routine blood counts Average probable duration of lymphocytosis was approximately 4 7 weeks the longest 7 weeks and the shortest 2 5 weeks In most cases

(6) Am J Dis Child 68 301 307 November

The articles in th s hapte leal w th agranulocytosis an l its relation hip to the toxic a t n f rtain drugs especially th ourac l The effect of eh m th ap spec ally p n c llin on the secondary infection n th c u l ti i probably of th gre te t therapeutic importan c —E l

Bone Marrow Changes in Case of Agranulocytosis

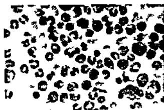
K Braun[4] (Rothschild Hadassah Univ Hosp Jerusa lem) reports results of serial bone marrow examina



Fi 66 (l ft) —F t t l p t J 6 1944 Th p l yt th l mph yt
Fi 67 (ght) —S d t l p n t J 9 1944 M j ty f ll r my l t l t d p m l yt

tions in a case of agranulocytosis apparently caused by sulfadiazine and sulfanilamide

Girl 18 rcce ved m l at n because f an a it l a teri l endoca dit s Thr e ternal pun tu es were ma le with i nin lays. Bone marrow examinat ons showed hypoplasia with pr dominance of lymph cytes ((per ent) (F g 66) changin to myeloid hyperplas a (49 p r cent young mvelo l cells (Fig 6) and finally reverting to normal w th only l ght hyperpla a of myeloid cells (Fig 68) Th se findings refl cted th linic l ourse After the second ternal pun ture temper tu e d cl ne l and bloo l count howed gradual



Fi 68 —Th d te l j tu J 14 1944 Sl ght h p pl f my l d ll

ncrease of leuko vte whi h ea h d a peak f 4 000 At this time th d fferential ount h w d a p udoleukem c pi ture w th 3 per ent mmatu e white cells After the th l st nal puncture the blood p cture became normal the patient r cove ed after 84 days

( ) A t m d t 3 1 0 1 J ly A g 1944

developing splenic enlargement roentgen changes in the lungs and leukocytosis and eosinophilia The spleen gradually recedes and fever disappears Roentgen appearance of the lung changes from one of scattered small foci to one of fibrosis and heavy hilar shadows The blood picture remains unchanged or becomes more abnormal and is probably the last feature to return to normal, sometimes persisting for years

Change in blood picture in the direction of increasing leukocytosis with a high eosinophil percentage constitutes the essential diagnostic criterion Total leukocyte count in this series ranged from 15 000 to 25 000 with eosinophils from 32 to 67 5 per cent Total eosinophil counts are more reliable for clinical comparison and prognosis than percentages Total eosinophil counts varied from 5 120 to 13 951 Morphology of eosinophils is normal Practically no myelocytes and immature cells are seen on blood smears Conversely the tendency is toward a shift to the right resulting in appearance of more cells with hypersegmented nuclei Eosinophils are mainly mature White blood cells other than eosinophils though showing lower percentages on differential count remain within normal limits in cells per cubic millimeter Erythrocyte count despite fever emaciation and illness remains practically normal In fact figures are generally higher than normal

Serologic study showed that this syndrome may be responsible for false positive reactions particularly in the Wassermann test Four of the seven patients tested had positive Wassermann reactions and negative Kahn reactions None of the seven had a history of syphilis or presented evidence suggesting its presence No specific organism has been demonstrated

From clinical findings alone this syndrome might be diagnosed as tuberculosis from hematologic findings as atypical leukemia and from serologic findings as syphilis Various arsenicals administered by several routes have been useful or strikingly effect e

cytosis It is thought that this complication occurs on the basis of developing sensitivity or idiosyncrasy rather than on cumulative effect of the drug The hemoglobin casts in the renal tubules may be accounted for on the basis of several rather characteristic transfusion reactions However renal complications following use of thiouracil have been reported

Agranulocytosis Following Thiouracil Administration Michael A Rubinstein[1] (Montefiore Hosp New York City) reports a case of severe agranulocytosis occurring during administration of thiouracil

Woman 47 had carcinoma of the thyroid (biop y) with bone metastases (radiologic evidence) She received a course of roentgen therapy and thiouracil was administered to observe its effect on the thyroid nodes Basal metabolic rates prior to this had been 4 and 0 per cent Dosage used was 0 2 Gm four times daily About six weeks later the thyroid nodes seemed softer and smaller and the patient had less pain. After ½ months of thiouracil administration the leukocyte count fell to 1 00 Despite discontinuance of the drug the count continued to drop and five days later reached its lowest level of 750 She was drowsy and depressed but not disoriented there were some anorexia and vomiting There was no fever and no necrotic lesions were present *in the mouth or throat* A *transfusion of 500 cc fresh whole* blood was given followed by another the next day Complete bone marrow and peripheral blood studies were done before transfusion and frequently afterward until normal values were obtained about a month later (Tables 1 and 2)

Agranulocytosis appeared to be the combined result of hypoplasia and lack of maturation of the myeloid series of the bone marrow While the total nucleated cell count was at the lower level of normal myeloid cells constituted hardly 13 5 per cent (normally over 75 per cent) Reticulo endothelial cells were not increased Arrest of maturation was evidenced by almost complete absence of segmented white blood cells in the bone marrow The predilection of thiouracil for white cells and bone marrow demonstrated by Williams and Bissel may be why the myeloid elements of bone marrow are more likely to be affected in cases of sensitivity to the drug

Return to normal of bone marrow changes preceded

(1) Am. J Cl P th 14 540 543 O t ber 1944

Braun believes that classification of agranulocytosis into a hypoplastic and a maturation type apparently is unjustifiable according to the findings in this case The hypoplastic marrow changed in three days into hyperplastic marrow with maturation arrest The latter change was the first indication of a good prognosis, since no granulocytes were present in the peripheral blood smear at that time The possibility exists however that an anaphylactic reaction which occurred after blood transfusion might have had some influence on the bone marrow

Confirmation of results in this case is desirable and Braun suggests that serial bone marrow examinations be made in every case of agranulocytosis

Fatal Agranulocytosis Resulting from Thiouracil M Irene Ferrer David M Spain and Richard T Cathcart[9] (Bellevue Hosp) report a case

Man 70 with severe hyperthyroidism received 0 2 Gm thiouracil four times a day the first three days then 0 1 Gm four times daily for the remainder of his hospital stay During 13 weeks he gained 31 lb and improved remarkably white blood cell count ranged from 5 100 to 7 400 He was placed on a maintenance dose of 0 2 Gm thiouracil daily and discharged to the outpatient department after 131 hospital days After 29 days dosage was cut to 0 1 Gm daily Seven days later a blood examination showed 1,250 leukocytes with 37 per cent polymorphonuclears He was immediately readmitted He felt well the first two days then his temperature rose and the fourth day was 105 F The fifth day there was pharyngeal inflammation which progressed in severity He died the seventh day Leukocyte count was 450 with no granulocytes on the day of death Pentnucleotide given intramuscularly and blood transfusions were of no avail Penicillin was administered during the last 24 hours without any effect on temperature or course

At autopsy besides evidence of pharyngitis pulmonary infection thyroid adenomas and cardiac dilatation the bone marrow in both hematoxylin and Giemsa s preparations showed moderate hypoplasia of granulocytic cells with definite decrease of mature polymorphonuclear leukocytes The kidneys contained hemoglobin casts in the collecting tubules

The dosage of thiouracil was somewhat higher than that now generally used It is problematic however whether total dosage was related to onset of agranulo-

(9) J A M A 1 7 646 647 Mar 17 1945

that of the peripheral blood In serial bone marrow aspirations there was gradual increase in myeloid cells coincident with a progressive shift to the right Simultaneously the leukocyte count showed an ascending curve though lagging behind recovery tracing of the bone marrow There was plenty of evidence that the anemia accompanying the agranulocytosis was not aplastic The erythroid marrow was hyperactive shown by marked increase of normoblasts and erythroblasts and presence of megaloblasts the peripheral blood showed signs of active regeneration (increased reticulocyte count polychromasia basophilic stippling) and there was a high platelet level

Agranulocytosis Treated with Penicillin Howard B Sprague and L Kraeer Ferguson (M C U S N R) *report a case*

Seaman ? was admitte l with sore throat prostration and t mperature of 104 S F six months after a six week course of treatment with a sulfonam de for gonorrhea Clinical course was haracteri t c of a severe attack of agranulocytosis with the white blood cell count reduced to 75 He was disoriented and had ulcerations of the throat and feet purpuric eruptions jaun lce and re urring massive abscess s on various areas of the body including the thighs feet face an area below the r ght apula and one below the left clavicle left axilla neck and ubpectoral region Penic llin therapy was started at once (20 000 units e ery four hours) with total dosage approximately 6 480 000 units He also received 36 blood transfusions pentose nucleotide ellow bone marrow and l ver extract

After 1 days the purpura an l jaundice had clea ed tempera t re was normal and blood stud es showed 8 900 white cells with per cent lymphocytes 10 per cent band forms 24 per cent gmented forms and 14 per cent mononuclears. On return of leukocyte production pus rap dly accumulated in the abscesses ve al large abscess s formed o ernight and appeared without preceding symptom Surgical drainage was necessary three times ther abs esses drained spontaneously Eventually skin grafts had t be appl ed to the les on on the legs

Penicillin apparently prevented generalized sepsis and septicemia It did not prevent appearance of localized abscesses but clinical experience indicates that a patient with such extensive local processes would probably have

( ) U S N M B U 43 1014 1016 N mbe 1944

TABLE 1.—SUMMARY OF BLOOD FINDINGS

DATE	WBC	MYEL	NON SEGM NEUTR	SEGM NEUTR	LYMPH	MONO	EOS	BAS	NORM BLAST
6/7	[illegible]		1	76	21	1	4		
6/8 thiouracil started									
6/14	6 [illegible]		[illegible]	[illegible]	[illegible]	4	[illegible]	4	
[illegible]	6 9[illegible]0		2	[illegible]4	16	1	[illegible]		
/12	4 7[illegible]0		8	[illegible]4	1[illegible]	[illegible]	[illegible]	1	
[illegible]	[illegible]800		6	53			4		
[illegible]	1 [illegible]00								
[illegible] thiouracil stopped									
8/[illegible]	[illegible]0	4	4	6	6[illegible]	1[illegible]	8		8/100
8/4	1 [illegible]00	4	12	[illegible]	60	10	[illegible]		6/100
8/6	1 [illegible]00	6	1[illegible]	12	44	12	4		4/100
8/1[illegible]	1 [illegible]00								
8 1[illegible]	[illegible],000								
8/18	4 400		2	54	4	[illegible]	2	1	
8/31	6 3[illegible]0			[illegible]2	[illegible]4	[illegible]	[illegible]		
9/16	[illegible]0		1	[illegible]8	2[illegible]	[illegible]	10	1	
[illegible]/21	9 000			6[illegible]	[illegible]1	[illegible]	5	1	

TABLE [illegible].—STERNAL MARROW STUDIES

Date	8/4	8/[illegible]	8/1[illegible]	8/[illegible]
Total nucleated cell count	4[illegible] 000	[illegible] 000	[illegible] 000	80 000
Megakaryocytes per cu mm	88	66	88	110
Differential count				
Myeloblasts	[illegible]	2 [illegible]	[illegible]	1 [illegible]
Promyelocytes	[illegible]	7 2[illegible]	[illegible] 2[illegible]	1[illegible]
Myelocytes neutrophilic	3 [illegible]	11 5	[illegible]	[illegible]
Myelocytes eosinophilic		0 [illegible]	1 [illegible]	1
Myelocytes basophilic		0 2[illegible]		
Non segmented neutrophils	1 [illegible]	8.2[illegible]	1[illegible] [illegible]5	1 [illegible]
Segmented neutrophils		0 2[illegible]	1[illegible] [illegible]	1[illegible]
Segmented eosinophils	0 [illegible]	1 [illegible]		[illegible]5
Basophils		0 2[illegible]		0.5
Lymphocytes	[illegible]	4.[illegible]	1[illegible]	[illegible]5
Hematogones		0.[illegible]	1 2[illegible]	1 2[illegible]
Plasma cells	0 [illegible]	0 [illegible]		1 5
Reticulum cell	0.[illegible]	0.5		
Monocytes	0 [illegible]			
Megaloblasts	1	0.[illegible]		
Erythroblast	3 [illegible]	2 [illegible]	4 [illegible]	[illegible]
Normoblast	[illegible]2[illegible]	4[illegible]	[illegible]0	1[illegible]
Total myeloid count	1[illegible].5	4[illegible].5	[illegible]	[illegible]6.2[illegible]
Total erythroid count	83.2[illegible]	52.5	[illegible]	1[illegible].5

cc blood she appeared acutely ill The left leg was swollen and there was a ragged superficial ulcer of the left thigh Pelvic examination revealed a foul smelling bloody vaginal discharge The blood showed moderate anemia and thrombopenia with pronounced leukopenia and complete agranulocytosis

Penicillin was administered for eight days with a total dosage of 800 000 units The next day after penicillin was started 1 000 cc whole citrated bank blood was given and the following day her condition was much worse Breathing became rapid there were vomiting and diarrhea the skin became cold and damp and tracheal rales developed Just before a second transfusion was given the white cell count rose suddenly to 18 500 and many primitive granulocytes were found in the stained smear The leukocyte count was 46 400 three days later and rose during the two subsequent days to 84 800 Primitive granulocytes were present in large numbers and there were occasional nucleated red cells. Leukocyte count gradually declined and she showed continuous clinical improvement She was discharged a week after the leukocyte count reached its peak when white cells had diminished to 16 900 Two weeks later the white count was 10 400 and she seemed completely well

In this case both interrupted and prolonged administration of sulfathiazole had been carried out The marrow reaction was evidently total since there was pancytopenia i e anemia leukopenia and thrombocytopenia

Death from agranulocytosis is not due to lack of granulocytes per se but to overwhelming sepsis which inevitably results when granulocytes disappear This furnishes a rational basis for treatment of agranulocytosis with sulfonamides to combat infection and prevent its spread Good results have been reported with sulfonamides in treatment of both primary and secondary agranulocytosis The situation in agranulocytosis due to a sulfonamide is somewhat different in that it seems unwise to add insult to injury and expect a good result However good results have been reported with use of another sulfonamide and even with the same preparation Hence it appears reasonably certain that the productive capacity of the marrow for granulocytes becomes re established spontaneously provided sepsis is held in check

Penicillin which evidently has little or no deleterious effect on bone marrow appears to be ideal for administration during a period of bone marrow injury particu

succumbed to septicemia had the infection not been checked

Agranulocytosis Treated with Penicillin Two cases of agranulocytosis apparently resulting from mapharsen injections for syphilis are reported by Leslie B Smith Frank Cohen and Ralph G Nichols[3] (M C A U S)

Two soldiers aged 18 and 31 were acutely ill on admission, the first had a severe sore throat and the second stomatitis In the first case the leukocyte count was 4 000 with no neutrophils and 95 per cent lymphocytes In the second case the leukocyte count was 5 370 with no neutrophils 74 per cent monocytes 10 per cent large lymphocytes and 16 per cent small lymphocytes

In the first case there was striking improvement within 4 hours after inauguration of penicillin therapy (20 000 units every three hours) 16 hours after the first dose the neutrophil count was 37 per cent Therapy was augmented on the fourth day by pentose nucleotide and yellow bone marrow and three small blood transfusions were given however the dramatic improvement was concurrent with administration of penicillin and preceded pentose nucleotide therapy

The second patient received 10 000 units of penicillin every three hours Granulocytes began to reappear in the blood on the second day and continued to increase this was accompanied by clinical improvement In addition to 380 000 units of penicillin, he received 30 capsules of yellow bone marrow and two transfusions of 250 cc citrated blood

From these striking results the authors believe that further trial of penicillin in treatment of agranulocytosis is indicated Apparently control of the secondary infection by penicillin allowed spontaneous leukocytic regeneration

Use of Penicillin in Treatment of Sulfonamide Agranulocytosis William Dameshek (Tufts Med School) and H C Knowlton[4] (Bangor Me) report a case

Woman 19 had received sulfathiazole for purulent vaginal discharge before and after delivery of a child about a month previously One week post partum phlebitis developed in the right leg and a few days later in the left leg Sulfathiazole was administered regularly 4 Gm daily for three weeks When temperature suddenly rose to 105 F sulfanilamide was substituted. Pronounced anemia leukopenia and granulocytopenia were discovered. When she was hospitalized after a transfusion of 1 000

(3) J A M A 126 10 7 1028 Dec 16 1944
(4) Bull. New Engl and M Center 7 14 148

It may be argued that spontaneous remissions occurred in these cases This is not unlikely in the second and third instances In the first instance however the usual supportive measures were carried out for over a week during which the condition became progressively worse The dramatic response within 48 hours following administration of pyridoxine in a dangerously ill patient is inconsistent with the usual conception of spontaneous remission in this disorder

The rapid and uniform response to pyridoxine leads the authors to propose that pyridoxine is the factor in liver and liver extracts responsible for the granulocytopoietic effect noted when liver is administered in agranulocytic angina and that it produces granulocytopoiesis by an effect on myelocytic elements of bone marrow It seems probable that pyridoxine is the factor involved in maturation and emigration of the polymorphonuclear leukocyte

[*Because of the serious nature of agranulocytosis multiple* therapeutic procedures are usually employed The authors procedure is no exception the offending drug was stopped and in two instances transfusions and pentose nucleotide were given in addition to pyridoxine Consequently even if the authors are correct in assuming that pyridoxine had a specific effect in the three instances occurring in two patients which they report their term uniform to describe the response hardly seems justified Until the difficult task of confirmation has been achieved we shall place our faith in the discontinuance of the offending drug and the prevention of secondary infection by sulfonamides and especially by penicillin —Eds]

Recent Studies on Yellow Bone Marrow Extracts J E Caldwell R H Sifferd J D Porsche and F Fenger[6] (Chicago) gave normal untreated albino rabbits comparable amounts of 15 unit U S P liver extract (Armour) cod liver oil whole milk concentrated carotene solutions and extracts of yellow bone marrow by intramuscular injection There was a comparable increase in absolute number and relative percentage of circulating granulocytes in four to six hours after injection response was similar and therefore nonspecific

Following modification of the procedure described by

(6) Am J M S 09 717 1 J e 1945

larly when that injury has been caused by a sulfonamide.

The leukemoid reaction during recovery, with presence of many primitive granulocytes, suggests that the marrow was filled during the period of agranulocytosis with many cells which could not enter the blood because of either maturation arrest or inhibited delivery In most patients with agranulocytosis, on recovery there is a sharp rise in leukocytes to levels of 15,000–25,000 with immature leukocytes in the blood However a count of 84,000 with large numbers of primitive cells including myeloblasts is rare and suggested to some observers the presence of leukemia, although the later course disproved this

Agranulocytic Angina Effectively Treated with Intravenous Pyridoxine (Vitamin B_6) Max M Cantor and John W Scott[5] (Univ of Alberta) report three instances of agranulocytic angina in two patients due to three different drugs which were successfully treated with a 10 per cent solution of pyridoxine hydrochloride in physiologic sodium chloride

In the first patient agranulocytic angina appeared after treatment with 4 Gm sulfathiazole over 24 hours Leukopenia and granulocytopenia persisted despite repeated blood transfusions and pentose nucleotide in large doses The disease appeared a second time the only previous medication being self administered aspirin One blood transfusion produced no effect In the second patient the disease developed about two months after use of thiouracil for hyperthyroidism 13 5 Gm being taken. The patient was treated only with pyridoxine Both patients were given pyridoxine hydrochloride intravenously in daily doses of 125–200 mg Temperature in each instance declined to normal and symptoms disappeared within 48 hours this improvement was associated with a leukocyte increase and reappearance of granulocytes in the blood Therapy was continued five to six days and blood examinations were performed for varying periods thereafter

(5) Canad M A J 52 368 371 April, 1945

iologic function of the normal spleen They labeled this disease primary splenic neutropenia They postulated the theory that the spleen has a selective destructive action on the various cellular blood components For instance in thrombocytopenia this selective destructive function destroyed the thrombocytes at an abnormally high rate, in hemolytic jaundice the erythrocytes were elected for destruction whereas in primary splenic neutropenia the neutrophils were the victim of this selective action In no instance was there interference with hemopoiesis as evidenced by normal bone marrow Splenectomy was performed on these patients with complete and permanent cure The present case fulfilled the criteria established by Wiseman and Doan and the spleen was removed early on the advice of Doan who studied slides of the blood and bone marrow

Primary Splenic Neutropenia H Milton Rogers and Byron E Hall[8] (Mayo Clinic) report a case in a woman 60 which fulfils the criteria established by Wiseman and Doan and also presents several features not previously observed There were evidence of hepatic disease as determined by grade 2 retention of dye in the sulfobromophthalein test gross changes in the liver at operation and chronic hepatitis with fatty degeneration on biopsy In the two years following splenectomy there has been no evidence of progressive hepatic disease On the contrary evidence of hepatic damage disappeared Hepatic function as indicated by the sulfobromophthalein method was normal Although hepatic damage increases risk of operation it does not contraindicate splenectomy and apparently does not decrease the prospect of ultimate cure Sections of the spleen in this case revealed no evidence of hyperplasia or phagocytic activity of the reticulo endothelium or of presence of free macrophages in the pulp

As in other cases of this type profound granulocytopenia myeloid hyperplasia of bone marrow splenomegaly and thrombopenia were observed for eight months prior

(8) A h Int Med 75 19 196 M b 1945

Kracke of subcutaneous administration twice daily of 1 cc of a solution consisting of five parts of benzene to one part of olive oil granulocytopenia developed in approximately 60 per cent of the rabbits in an average period of 10 days Rabbits poisoned thus by benzene and given daily doses of 15 unit liver extract cod liver oil whole milk or concentrated carotene solutions intramuscularly for 14 consecutive days showed no evidence of physical, leukocytic or clinical response Similarly poisoned rabbits that received comparable doses of yellow bone marrow extracts showed immediate response and complete physical, leukocytic and clinical recovery by the fourteenth day

The conclusion is that extracts of yellow bone marrow contain a specific substance or substances which stimulate leukopoiesis in rabbits poisoned by benzene

[This seems to be a well controlled study and deserves careful attention and confirmation

The next two articles discuss primary splenic neutropenia a syndrome or condition which deserves recognition because it constitutes the most recently recognized entity in which splenectomy is beneficial or curative —Eds]

Primary Splenic Neutropenia Moses Salzer, J Louis Ransohoff and Herman Blatt[7] (Cincinnati) report a case in which splenectomy was done early in the disease

Woman 59 displayed no secondary anemia of any consequence no diminution in platelets and no jaundice, signs reported in previous cases of more prolonged illness Before splenectomy she showed a tendency to repeated infections doubtless due to a low leukocyte count but particularly to a low polymorphonuclear count Pneumonia developed during hospitalization, and she responded promptly to sulfadiazine therapy although total white blood cell count at that time was only 800 Splenectomy was performed about a month later and prompt and complete recovery after operation was in striking contrast to the slow convalescence and incomplete restoration of health following pneumonia 11 months before

Just before splenectomy there were erythrocytes 3 790 000 per cu. mm leukocytes 1 400 polymorphonuclears 22 per cent lymphocytes 51 per cent and monocytes 17 per cent At the time of report she was in perfect health with normal blood values

In 1942 Wiseman and Doan reported five cases of neutropenia resulting from a pathologically altered phys

(7) Ann Int Med ? 71 ?73 F bra y 1[illegible]

iologic function of the normal spleen They labeled this disease primary splenic neutropenia They postulated the theory that the spleen has a selective destructive action on the various cellular blood components For instance in thrombocytopenia this selective destructive function destroyed the thrombocytes at an abnormally high rate in hemolytic jaundice the erythrocytes were elected for destruction whereas in primary splenic neutropenia the neutrophils were the victim of this selective action In no instance was there interference with hemopoiesis as evidenced by normal bone marrow Splenectomy was performed on these patients with complete and permanent cure The present case fulfilled the criteria established by Wiseman and Doan and the spleen was removed early on the advice of Doan who studied slides of the blood and bone marrow

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(8) A h I t Med 75 19 196 Ma h 1945

to splenectomy Normal leukocyte and platelet counts were established after operation and the patient's health has remained excellent

While the clinical syndrome of primary splenic neutropenia seems well established microscopic appearance of the spleen does not seem to be constant Other investigators have expressed the opinion that excessive destruction of neutrophils in the spleen is the cause of neutropenia but absence of increased phagocytic activity of the reticulo endothelium in two of the eight cases reported raises the question of some other etiologic mechanism Moore and his associates hypothesized concerning the existence of a substance termed a leukolysin which was formed in the spleen and caused suppressed leukopoiesis in the bone marrow Although the marrow appeared to be more cellular after splenectomy than before they felt that this change migh be due to error inherent in the technic of sternal puncture However the authors believe that formation of leukolysin in the presence of this syndrome has not been disproved

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LEUKEMIAS

Leukemias are discussed by F K Miller and D L Turner[9] (Jefferson Med College) All leukemias are disorders of blood forming organs rather than of peripheral blood, so that leukopenic or normal white blood cell counts are compatible with the term leukemia Presence of abnormal cells in the blood is more important than level of leukocytes

There is little experimental and no clinical evidence that human leukemia in any form is caused by bacterial or filter passing organisms Work on leukemia and tumors in mice stresses genetic and hereditary characteristics In mice whether leukemias are spontaneous or are caused by a carcinogenic agent their transplantation depends on transfer of living cells to the new host Because of these animal experiments human leukemias are

(9) M Cl N rth Am ca 8 13 6 138 N em

thought to be neoplasms but the experiments offer no clue to the cause of the human disease As for the metabolic theory there is evidence that the adrenal inhibits lymphopoiesis and stimulates myelopoiesis Other evidence of hormonal or metabolic controls of blood forming organs may be found in control of myeloid tissue by the antianemia factor of liver in the relation of lymphoid hyperplasia to hyperactivity of the thyroid and in increased incidence of lymphoid tumors in animals receiving various steroid hormones

The authors found two specific substances in varying proportions in urine of patients with acute and chronic myeloid leukemia acute and chronic lymphoid leukemia Hodgkin s disease monocytic leukemia and lymphosarcoma The myeloid substance was a keto acid and the lymphoid substance a hydroxy acid and they apparently were closely related chemically These specific substances can also be extracted from the lipoid fraction of normal beef liver

In guinea pigs receiving these extracts or fractions of them the myeloid substance stimulates myelopoiesis i e proliferation without maturation The lymphoid substance inhibits proliferation of myeloid cells and hence allows them to mature It causes lymphoid proliferation without maturation while the myeloid substance inhibits proliferation of lymphoid cells and maturation occurs Normally the two substances are balanced in action and therefore regulated hemopoiesis occurs It is postulated that an excess of myeloid substance occurs in chronic myeloid leukemia together with at least a normal (evidence favors a slight excess) amount of lymphoid substance Hence the disease runs its course with greater than normal maturation of myeloid cells As lymphoid substance becomes exhausted an acute exacerbation occurs characterized by proliferation of myeloid cells without maturation Death follows with the disease in an acute or blastic phase Chronic lymphoid leukemia may be explained similarly The two acute diseases acute lymphoid and acute myeloid leukemia may be explained

as deficiencies of one or the other maturating substance

Human leukemia may occur without precursors, but in many cases it follows a precipitating incident or incidents such as trauma exposure to radiation exposure to benzol or its derivatives use of arsenical or sulfonamide drugs various infections etc Apparently these incidents and agents upset the balance of normal hemopoiesis

Most cases of chronic myeloid or lymphoid leukemia are not difficult to diagnose Greatest difficulties in diagnosis are encountered in acute leukemias, although any case of leukemia may present a problem if the leukocyte count is leukopenic or normal However many cases show a preponderance of primitive or blast cells and special laboratory procedures will usually differentiate whether they are lymphoid myeloid or monocytic types

Treatment is at best only palliative although most patients can be made comfortable and many can be helped to live out their last few months or years fairly normally Radiation from such sources as x ray, radium or radioactive phosphorus arsenic in the form of Fowler's solution or sodium cacodylate transfusions and vitamins constitute the major therapeutic agents Irradiation of some type is usually indicated in chronic myeloid leukemia and often in chronic lymphoid leukemia particularly if there is anemia and extensive lymph node enlargement In acute leukemias irradiation is usually contraindicated except when nerve or bone pain may be relieved thereby

Histopathologic Explanation for Oral Lesions in Acute Leukemias is presented by Lester W Burket[1] (Univ of Pennsylvania) based on postmortem study of oral tissues from a boy 12 who died of acute monocytic leukemia General pathologic diagnosis was generalized lymph node enlargement hyperplasia of the bone marrow splenomegaly and multiple petechiae in the skin conjunctivas scleras pleurae liver and kidneys as well as necrotizing gingivitis

(1) Am J Orthodont 30 516 5 3 Sept mb r 1

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(1) Am J Orth dont 30 516 5 7 September 1944

kin s paragranuloma is extremely variable Sometimes signs or symptoms suggesting a transition to granuloma develop and death ensues in a short time In others many months or several years elapse before development of Hodgkin s granuloma In still others the condition remains quiescent many years and death may be due to intercurrent disease or the patient may remain in excellent health for many years In these last cases however there is always the possibility that the disease will become active again or that Hodgkin s granuloma will develop Involvement of mediastinal lymph nodes does not necessarily imply that Hodgkin s granuloma is developing but enlargement of the spleen is an ominous sign Onset of systemic symptoms such as fever weakness anorexia or weight loss almost always indicates a transition to the granulomatous form There is no characteristic blood picture although increase in polymorphonuclear neutrophils is found occasionally There is no anemia

The character of symptomatology of Hodgkin s granuloma is extraordinarily protean In most cases painless enlargement of one or more cervical lymph nodes is the first symptom but any system may appear primarily implicated Often moderate lymphadenopathy is already present at the time of or increases after a respiratory infection so as to demand medical attention

The enlarged lymph nodes early are rarely painful unless they press on nerves or are adjacent to obvious septic foci Later pain due to lymphadenopathy is more frequent particularly in the groin or axilla The overlying skin usually appears normal and the nodes are seldom fixed to surrounding structures although they may become immobile because they fill the entire neck and impinge on contiguous fixed structures The nodes are usually firm and rubbery occasionally soft and rarely hard In most cases the involvement is bilateral when the patient is first seen although almost invariably one side is involved much more than the other No particular part of the cervical region appears to be most frequently in

bosis of the gingival vessels explains why the necrosis is so extensive and why it is not accompanied by any marked inflammatory reaction Hypertrophy of these tissues results from the large extravascular leukocytic infiltration (Fig 69) and secondary changes common to any infarcted area Rapid loosening of teeth results from early necrosis of dental periosteum The "woody, artificial feel of the teeth is due to extravascular accumulation of mononuclear cells in the dental periosteum Marked 'tightening of teeth which accompanies periods of therapeutically induced remissions can be explained by disappearance of leukocytic infiltration from the dental periosteum and possible reattachment of dental periosteal fibers to the alveolar bone

These histopathologic studies afford no explanation for the spontaneous pulpal and periapical "abscesses so often observed In view of recorded pulpal changes it is probable that spontaneous abscess formation is due to secondary infection of focal areas of liquefaction necrosis of the dental pulp and periapical tissues resulting from thrombosis of nutrient vessels or actual strangulation of pulpal tissues due to a massive leukocytic infiltration The extravascular collection of large mononuclear cells in the pulpal tissue especially beneath the odontoblastic layer affords a ready explanation for odontalgia

Hodgkin s Disease Symptoms and Course of the three types are discussed by Henry Jackson Jr and Frederic Parker Jr (Harvard Univ)

Hodgkin s paragranuloma is comparatively benign, with onset nearly always heralded solely by painless lymphadenopathy usually cervical System symptoms are absent at first and the patient appears in good health Approximately 20 per cent of cases progress after months or years to Hodgkin s granuloma Insidiousness of onset in no way precludes this development and cases that progress cannot, even by most careful histologic study be distinguished in their incipiency The course of Hodg

( ) New England J Med 231 639 646 Nov 9 19

unrelated to meals and is occasionally accompanied even early by loss of weight Superficial lymph nodes are often painful (rarely the case in granuloma) Weakness dyspnea cough and vomiting may be seen early with rapid loss of weight The disease runs an insidiously rapid course even though initial response to roentgen therapy may appear to be good Fatigue and rapid weight loss are frequent Most patients have pain referable to the organs or tissues involved and involvement of the lung with cough is frequent Fever is rare (in contrast with granuloma) Hodgkin s sarcoma runs the course of a highly malignant neoplasm

Acute Plasma Cell Leukemia Leo M Meyer Jacob Halpern and Faith N Ogden[3] (Kings County Hosp Brooklyn) review the literature on multiple myeloma with plasma cells in the circulating blood and also cases reported as acute plasma cell leukemia

Of new growths involving plasma cells solitary extramedullary plasmacytomas with and without subsequent involvement of distant organs or bone marrow constitute a distinct and separate group The course of these tumors may be either benign or malignant There are also single plasma cell tumors originating in bone marrow

Multiple myeloma is the most frequent disease involving new growths of plasma cells The classic picture is that of diffuse involvement of ribs sternum vertebrae skull pelvis and humerus in a neoplastic growth arising in the bone marrow with resulting nodule formation Included in this group are cases of multiple myeloma in which plasma cells were found in the circulating blood

Finally there is a small group of cases in which there is the clinical course of leukemia with diffuse organ and bone marrow invasion by plasma cells but no apparent bone marrow nodule formation The authors believe however that these case also were instances of multiple myeloma with plasma cells in the circulating blood

The authors report a case which they believe fulfils all the criteria of acute leukemia

(3) A I t Med 585 598 April 1945

volved Enlarged lymph nodes elsewhere as in the axilla groin and inguinal regions generally have the same characteristics as those in the neck but are more prone to be painful and only rarely fluctuate in size

Pain is the next most frequent initial complaint, but early in the course of Hodgkin's granuloma it is comparatively rare In Hodgkin s and reticulum cell sarcoma pain is often an early and almost constantly a late symptom The most frequent sites of pain are the abdomen and back Abdominal pain is usually caused by retroperitoneal lymph nodes and only rarely to invasion of one of the abdominal viscera or to great enlargement of the spleen Back pain may be due to various causes enlarged lymph nodes pressing on spinal nerves, direct involvement of vertebral bodies or granulomatous lesions in the dura or epidural space Pain in the chest, shoulder groin leg or axilla is occasionally encountered as an initial symptom usually in such circumstances there is unequivocal evidence of Hodgkin s granuloma

Generalized weakness may be the first symptom and without obvious lymphadenopathy or splenomegaly may be difficult to evaluate Sometimes gastro intestinal symptoms appear first Initial signs and symptoms may also include anorexia edema of the legs dyspnea weight loss abdominal masses cough generalized itching amenorrhea hemoptysis persistent sore throat vomiting hematemesis dysphagia melena and deafness

In most cases Hodgkin s granuloma progresses to fatal termination but the course is extremely variable and it is impossible in any given case to make a definite prognosis The clinical course depends on the extent and rapidity of spread and the organs involved Hodgkin granuloma only rarely progresses sharply into Hodgkin's sarcoma a far more malignant form Such transformation is far less frequent than the comparable progression of Hodgkin s paragranuloma into Hodgkin s granuloma

Pain is the most usual initial symptom of Hodgkin's sarcoma It is most frequent in the sually

iliac region which was painful on pressure Urinalysis disclosed .. plus albumin with many hyaline casts and leukocytes Initial blood count showed 55 per cent hemoglobin 2 140 000 erythrocytes 31 000 leukocytes 30 per cent segmented polymorphonuclears 6 per cent nonsegmented polymorphonuclears, 2 per cent myelocytes 11 per cent lymphocytes 7 per cent monocyte and 44 per cent plasma cells Two subsequent blood examination showed reduction of plasma cells to 5 and 3 per cent with relative increase in polymorphonuclear cells and actual decrease in leukocytosis Serial bone marrow studies showed 48 7 0 and 1 per cent plasma cells Bence Jones protein was absent from the urine Total blood proteins were 11 Gm per cent of which 5 Gm was albumin and 8 5 Gm globulin Lumbar puncture and complete skeletal roentgenograms revealed no abnormalities

Signs of bronchopneumon a developed three days after admission sulfathiazole was administered The patient was drowsy and slept most of the time Later she complained of pain in the abdomen She was obviously icteric The gums were oozing and swollen and purpuric spots appeared over the body Axillary nodes became enlarged Signs of consolidation became more pronounced Three transfusions of 500 cc each were given but death occurred 18 days after admission

Cells d signated as plasma cells in peripheral blood and bone marrow were of several types Many were typical being slightly larger than the lymphocyte and having a deep blue cytoplasm and a clear zone opposite the eccentr cally placed nucleus Some nu lei had the typ cal cartwh el structure others showed a thick dense irregular chromatin Other cells were slightly la ger the cytoplasm varying from p nk to bluish gray and had a slightly larger nucleus also e centric these cells resembled atypical normoblasts and erythroblasts The nuclei resembled those of the typical plasma cell (Figs 71 and 72) Finally some cells were two or three times the size of the usual lymphocytes their nu lei were large occasionally oval but usually round and finely granular with one to three nucleol The cytoplasm was deep blue and had a thin clear perinuclear zone These cells were considered immature plasma cells closely resembling megaloblasts

At autopsy the spleen showed diffuse infiltration of plasma cells into the sinusoids m xed with pulp cells. Bone marrow was hyperplastic with apparent increase of plasma cells In the liver there was infiltrat on into portal spaces and sinuses consisting of round plasma and reticulo endothelial cells Parenchymal cells showed evidence of extensive fatty changes Normal architecture of lymph nodes was completely destroyed and replaced by an overgrowth of small round and plasma cells which had infiltrated into surrounding fat There was no evidence of infiltration into other organs

Woman 67 had had numerous attacks over 20 years of dependent edema and dyspnea For four weeks she had had severe frontal headaches dizziness and periods of unconsciousness, she

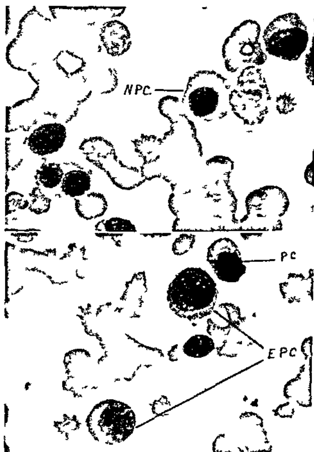


Fig 71 (top) —N m blast type plasma ll educed f n × 1 000
Fi 7 (bott m) —Eryth obl t c type plasm lls d ed from × 1 000

had lost 9 lb and coughed up a little blood and recently had complained of pain across the chest Positive physical findings were apparent severe anemia ptosis of the left eyelid enlarged cervical and inguinal node and a round movable mass in the right

the significance of plasmocytosis in multiple myeloma (1) true leukemia and (2) a plasmocytic reaction in the blood (analogous to a leukemoid reaction) caused by essentially localized tumors

Rubinstein reports a case in which examination of the peripheral blood disclosed atypical plasma cells which suggested the diagnosis before other tests were per formed Subsequently the blood picture of plasma cell leukemia developed

Woman 58 complained of abdominal and low back pain and dysphagia Two years before there had been a sudden profuse rectal hemorrhage requiring several blood transfusions Its cause could not be ascertained despite detailed examination From this period on there were progressive weakness and pallor The low back pain appeared two months before admission and she soon became incapacitated

The blood count showed pronounced anemia of hypochromic type hemoglobin 31 per cent red blood cells, 1 900 000 leuko cytes 6 000 platelets 90 000 per cu mm Differential count was normal except for an occasional atypical plasma cell Sternal mar row aspiration confirmed the diagnosis revealing 56 per cent plasma myeloma cells other elements were remarkably reduced The blood serum showed an immediate positive formol gel re action Using the ordinary heat test at pH 5 the urine was found to contain large quantities of Bence Jones proteose and to be consistently free from albumin There were occasional hyaline and granular casts Urinary concentration tests showed a specific gravity of 1 012–1 015 Urea clearance was 11 per cent Roentgen examination of the skull showed numerous circular lesions through out bones of the calvarium There were numerous areas of bone destruction of the lower ribs lumbar vertebrae and pelvis and a pathologic fracture of the body of the first sacral vertebra

There was progressive increase (absolute and relative) of plasma cells coincident with a rise of total white cell count and fall of neutrophils. During hospitalization the patient had considerable back pain radiotherapy brought no relief She received several blood transfusions Aspiration of small soft bright red nodules at the back of the tongue revealed 6 per cent plasma cells where as at that time there were only 1? per cent plasma cells in the peripheral blood The course was progressively downhill and death occurred two months after admission Postmortem examina tion was not obtained

In retrospect it is probable that the initial symptom of rectal bleeding was due to thrombocytopenia conditioned by plasma cell infiltration of the bone marrow The ear

Numerous authors have stressed the relationship of diffuse multiple myeloma and lymphatic and myelogenous leukemias. This becomes even more apparent when patients with diffuse myelomatous tumors begin to show plasma (myeloma?) cells in the circulating blood. The present case completes the chain in the analogy to lymphoid tumors in that no masses were demonstrated in any bone either by complete skeletal roentgenograms or after careful search at autopsy. The elevated blood globulin with the diffuse invasion of organs, including lymph nodes and bone marrow and immature and mature plasma cells in the circulating blood, justifies the designation of acute plasma cell leukemia.

Plasma Cell Invasion of Peripheral Blood in Multiple Myeloma. Michael A. Rubinstein[4] states that the possibility of passage of myeloma cells from the bone marrow into the peripheral circulation has not been universally acknowledged. However, in many cases reported as multiple myeloma plasma cells were found in the peripheral blood. The typical plasma cell has little significance in diagnosis of myeloma as it may be seen in other conditions (rubella, infectious mononucleosis, etc.) but atypical cells are important when found in blood smears. Plasma myeloma cells are much larger than typical plasma cells, the cytoplasm is considerably greater, does not assume the deep basophilic staining quality with Giemsa's stain and does not show the characteristic stain with Pappenheim's methyl green pyronin. Myeloma cells show myeloid characteristics whereas genuine plasma cells resemble lymphocytes. The oxidase reaction is negative in plasma cells but is present in granular cells of myelocytic myeloma. In supravital preparations plasma cells show an eccentric nucleus and a clear homogeneous cytoplasm. Large dense mitochondria appear around the nucleus. Failure to differentiate between these types of plasma cells is a chief cause of disagreement concerning plasma cell leukemia.

In general, two concepts have been advanced to explain

(4) J. Mt. Sinai Hosp. 1 616 6 3 May June, 1945.

suggest that this case was chronic or subacute rather than acute leukemia

A survey of this case and of the 12 somewhat similar cases reported as eosinophilic leukemia brings out certain significant features Twelve patients were males aged 11–48 although five were under 20 when symptoms began Four cases were acute eight chronic and one unclassified Weakness was a complaint in seven prostration in three and gastro intestinal disturbances in five Lymph node enlargement was noted in 10 and discovered in 2 others at autopsy Splenomegaly was noted clinically in 10 and in 1 other at autopsy Hepatomegaly was present in eight hemorrhagic manifestations were found in five Five were edematous Fever was not encountered Irradiation and administration of Fowler s solution caused marked decrease in leukocytosis Increase in leukocytes but some clinical improvement followed splenectomy Death was usually from exhaustion

Anemia was present in 10 usually terminally but was severe in only 2 Total white count was nearly always high reaching 65 000–312 000 in every case except one (16 000) Mature eosinophils were usually typical with segmented nuclei and densely refractile granules Vacuoles in the cytoplasm and granules of irregular size and abundance have been described In the present case adult eosinophils were of normal appearance but in myelocytes and metamyelocytes quantity and maturity of eosinophilic granulations were not always in the same stage of maturity as were the nuclei The most common hematologic change has been migration of immature cell forms—myelocytes metamyelocytes and stab cells—into the blood stream Infrequently these have been numerous (up to 73 per cent of total eosinophils in one instance) In another case 90 per cent of circulating leukocytes *were judged to be primitive myeloblast forms* In several others immature cells represented 0 5–5 per cent of the differential count However in fully half the cases no immature cells were seen in the circulating

her diagnosis of albuminuria in this case is a common error and stresses the importance of careful urinalysis. Reduction in kidney function and azotemia may be ascribed to a "myeloma kidney." This case emphasizes the relationship between plasma cell leukemia and multiple myeloma

Eosinophilic Leukemia Marion Friedman, Irving J Wolman and Harlan H Tyner[5] (Norfolk, Va) believe eosinophilic leukemia loosely interpreted, may not be as rare as the meager number of reported instances suggests Doan and Reinhart, analyzing 317 cases with leukemic syndromes classified 3 as chronic eosinophilic myelogenous leukemia and described one other, with both eosinophilic and basophilic granules in the same malignant myelocytes as "mixed" chronic myelogenous leukemia Lack of certainty attending diagnostic interpretation of leukemia with eosinophilia prompts the present case report

Negro boy, 11 was judged to have had chronic myelogenous leukemia eosinophilic variety because he showed the major nosologic manifestations of leukemia He suffered from weakness cachexia and weight loss progressing to death Leukocyte count was 126 000–194 000 80–9? per cent of white cells in the circulation were eosinophils nearly all mature although occasional young or abnormal forms were demonstrable Bone marrow lymph nodes pelvic fascia thigh and back muscles salivary glands lungs stomach nasal mucous membrane and other tissues were infiltrated with myeloid accumulations of eosinophils No other disorder that occasions high eosinophilia was known to be present On two occasions hypoproteinemia with dependent edema probably secondary to dysfunction of the enlarged liver was promptly relieved by intravenous administration of blood plasma

Absence of splenomegaly marked anemia architectural destruction of spleen and lymph nodes hemorrhages and thrombocytopenia is not sufficient to invalidate the diagnosis these features are not universal in any variety of human leukemia Although symptoms had been observed only five months absence of anemia persistence of platelets at or near normal and failure of marrow to show infiltration with primitive blast forms

(5) Am. J M Sc 08 333 343 September 1944

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blood Various organs may be infiltrated by proliferating eosinophilic myeloid tissue

Hematologic Complications of Therapy with Radioactive Phosphorus are discussed by Louis A Hempelmann Jr Edward H Reinhard, Carl V Moore, Olga S Bierbaum and Sherwood Moore[6] (Washington Univ)

Of 116 patients with various types of hematologic dyscrasias treated with radioactive phosphorus 100 were observed long enough for evaluation of therapy Anemia leukopenia and thrombocytopenia developed frequently In most cases there was excellent evidence that these complications were the result of therapy and not manifestations of the disease They often appeared weeks or several months after the last injection of radioactive phosphorus Since excessive exposure to radium and x rays is known to cause toxic effects on the bone marrow, these complications are not unexpected

Radioactive phosphorus was used as an isotonic solution of the dibasic sodium salt Plan of treatment for all diseases except polycythemia closely followed the 'fractional method' outlined by Low Beer Lawrence and Stone Each dose given parenterally varied between 100 and 2 000 microcuries As the leukocyte count approached normal in patients with leukemia or became subnormal in cases in which it was not elevated before treatment dosage was decreased and time between treatments was lengthened Patients with polycythemia were given larger quantities of radioactive phosphorus at much less frequent intervals

Incidence of thrombocytopenia leukopenia and anemia is summarized in the table The usual pattern was first a fall in white cell count then in platelets and finally in erythrocyte level However, platelets occasionally fell to extremely low levels even in patients in whom leukopenia or anemia did not develop Thrombocytopenia and anemia frequently appeared as late manifestations even weeks after therapy had been discontinued

(6) J Lab & Clin Med 29 10 0 1041 October 1944

INCIDENCE OF ANEMIA LEUKOPENIA AND THROMBOCYTOPENIA IN 100 PATIENTS

	TOTAL CASES	ERYTHROCYTES		LEUKOCYTES		PLATELETS		
		Dec e sed 1 000 000 o M (t <3 5 m p C Mm)	I d 1 000 000 o M p Cu Mm	Le k p (F ll to L Th n 3 000 per C Mm)	I t l C t < 000 p t >6 000 per Cu Mm	Th mb t p: F ll t <100 000 b t >50 000 p r Cu Mm	Th mb t p: F ll to <50 000 p Cu Mm	I ed by Mo Th n 00 000 p C Mm
Polycythemia vera	18	4	0	[illegible]	0		1	3
Myelogenous leukemia	[illegible]	8	10	7	0	1	10	13
Lymphatic leukemia		7	0	5	0	6	6	
Leukosarcoma	13	9	1	8	2	1	9	
Monocytic leukemia	4	0	0	0	0	0	0	0
Plasma cell myeloma	6	2	0	4	0	0	3	1
Lymphosarcoma	2	0	0	1	0	0	0	1
Ret culum cell sarcoma	3	[illegible]	0	3	0	0	[illegible]	0
Hodgkin s disease	6	3	0	3	0	0	[illegible]	0
Giant follicular lymphoblastoma	1	1	0	1	0	0	0	1
Total	100	36	11	41		10	3	[illegible]3

Thirty eight of the patients with thrombocytopenia appearing after therapy showed clinical manifestations of abnormal bleeding, and in one patient with polycythemia and severe neutropenia an angina like lesion developed on the lower lip Weakness and fatigue appeared in several subjects whose red cell count fell to anemia levels At autopsy localized areas of necrosis in the bone marrow were observed several times In four cases the marrow was found to be aplastic in three of leukosarcoma and one of Hodgkin s disease

Description of these hematologic complications is not intended to deprecate the therapeutic value of radioactive phosphorus In almost all cases there was prompt recovery from thrombocytopenia and leukopenia with slow recovery from anemia apparently induced by the isotope The only exceptions occurred among patients obviously in the terminal stages This experience confirms the conclusions of others that radioactive phosphorus induces excellent remissions in patients with polycythemia vera, chronic myelogenous leukemia and chronic lymphatic leukemia Results are at least as good as those obtained with other forms of radiation they may prove better Since however it is important to understand the dangers as well as the limitations of any new therapeutic technic, occurrence of hematologic complications should receive emphasis particularly because production of irreversible damage to the hemopoietic organs may be avoided if they are recognized and further therapy is withheld

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PURPURA FIBRINOPENIA AND HEMOPHILIA

Thrombocytopenic Purpura in Pregnancy Because of its rarity little is known about this condition Burnett and Klass in 1943 found records of only 68 cases They considered 46 doubtful, 18 as representing symptomatic purpura and only 4 as true thrombocytopenic purpura They reported an additional case which they regarded as the fifth true case recorded William F

Finn[7] (Cornell Univ) describes these five cases and adds five more from the literature and reports three which were seen among 43 334 patients delivered at New York Hospital

CASE 1—Negress 17 had had repeated episodes of bleeding from the gums Ten years previously her platelet count was 6 400 Until three years previously she improved on rest and transfusions but at this time after failure to improve and a decrease in platelets splenectomy was done Improvement was gradual In the fifth month of pregnancy three years after splenectomy she again noted bleeding from gums dizziness fatigue and dyspnea Rapid improvement followed several transfusions administration of feosol and citrus pectin and a high vitamin diet Bleeding from the gums recurred a month before delivery and she was hospitalized A 5 0 Gm infant was delivered spontaneously at term with blood loss of ?0 cc Bleeding from the gums stopped almost immediately after delivery but blood destruction continued The puerperium was complicated by intra uterine infection treated by penicillin No signs of purpura developed in the infant and analysis of blood and spinal fluid revealed no evidence of internal bleeding

CASE —Girl at age 6 had gastric hemorrhages at 14 there were profuse menses followed by petechiae and the platelet count was ?0 000 After splenectomy it was 100 000 and bleeding time 10 minutes Nine years later in the first pregnancy there were occasional nosebleeds one month before term and the platelet count fell to 45 000 The infant died the third day after delivery of multiple internal and subcutaneous hemorrhages Two years later a spontaneous abortion occurred at three months In the third pregnancy the following year the tourniquet test showed numerous petechiae at three months Blood loss at delivery of a 3 00 Gm infant was 100 cc The infant had purpura one hour after delivery but no bleeding developed The platelet count was 40 000 bleeding time more than 90 minutes and clot retraction absent Sternal aspiration showed decreased megakaryocytes and failure of platelet production After multiple transfusions the child improved six weeks after delivery no bleeding had occurred purpuric spots had disappeared and the bleeding time was three minutes

CASE —Girl at age 1? had an induced labor in the seventh month because of eclampsia In the second pregnancy the following year though partial premature separation of the placenta occurred a living 1,500 Gm infant was delivered Five years later the patient noted bleeding from the gums vaginal hemorrhage and ecchymoses The platelet count was 10 000 bleeding time

(7) Am J Obst & Gynec 48 49 ?? Oct 1944

over 30 minutes clot retraction defective, and tourniquet test positive The bone marrow was normal After splenectomy all bleeding ceased and the platelet count rose to 360 000 In the fifth month of the third pregnancy (2½ years after splenectomy) platelets numbered 520 000 and bleeding time was one minute Blood loss at delivery was 450 cc Both infant and mother were discharged well

Hereditary Hemorrhagic Telangiectasia a rare disease first recognized by Osler is characterized by the triad of multiple telangiectases hemorrhage or anemia and a history of familial occurrence Some 500 cases occurring in over 100 families have been described Characteristic lesions consist of pinpoint to pea sized telangiectases occurring most commonly in skin and mucous membranes but also in various organ systems These telangiectases represent dilatation of blood vessel walls which consist of a single layer of endothelium covered with a greatly thinned layer of epithelium The lesions commonly appear in mucous membranes about the end of the first decade of life and in the skin during the third and fourth decades

Extreme fragility of the lesions and time of their appearance largely determine symptomatology As the nasal mucous membrane is usually involved first epistaxis occurs with increasing frequency after late childhood In middle life skin and visceral lesions appear and add to the blood loss The resulting secondary anemia may be severe but hemoglobin is seldom below 50 per cent Skin lesions occasionally disappear after a period of years but anemia persists As the patient ages the quantity of blood lost increases and hemorrhage from the nose of 1 000–1 500 cc is not uncommon The 6 per cent mortality is associated with these hemorrhages

The hereditary factor apparently is a simple dominant transmitted by and affecting both sexes Occurrence of atavism in this disease has also been stressed

Glenn Q Voyles and James O Ritchey[8] (Indianapolis) report two cases in men 51 and 70 Both patients had hemoglobin levels lower than those usually described

(8) Ann Int Med 2 730 736 May 1945

In the first case hemoglobin was 5 8 Gm at first examination and 18 months later was 6 5 Gm During seven years the second patient was followed hemoglobin ranged from 3 2 to 10 5 Gm but usually was between 5 5 and 7 5 Gm with red cell counts between 2 500 000 and 3 000 000 Both patients had lesions in skin mucous membranes upper respiratory tract and colon In the first case the skin contained numerous telangiectases most abundant on the upper half of the face and ears and the finger tips but also present on the back arms legs left great toe prepuce and glans penis Telangiectases were also noted in the mucous membranes of the nose throat and tongue In the second case telangiectases were present in the skin of the face scalp ears chest back legs glans penis palms of the hands sides of the fingers and toes being most abundant on the face ears and fingers Similar lesions were seen in the mucous membranes of the mouth palpebral conjunctiva and nose The second patient had microscopic hematuria on rare occasions

Although various forms of treatment have been advocated none seems to be satisfactory Cauterization of bleeding points and radium packs have been advocated to control epistaxis Application of these treatments in Case 2 resulted in necrosis of the septal cartilage and bleeding continued especially from small arteries coming up through the floor of the nose It has also been suggested that if anemia is adequately controlled the telangiectases will regress This was not true in the authors cases and it was impossible to maintain an adequate hemoglobin level except by frequent transfusions Hence treatment was symptomatic pressure packing to control hemorrhage and ferrous sulfate for anemia Use of thromboplastic substances seemed to reduce the frequency of hemorrhage although there is apparently no physiologic basis for this improvement

As only one brother and the eldest son of the first patient could be examined and the source of the father s hemorrhage could not be determined it was impossible to determine whether this represented an instance of

atavism The brother and son showed no telangiectases and none of the patient's family had frequent epistaxis or similar skin lesions However as his children grow older one or more of them may develop evidence of the disease The mother of the second patient had telangiectases and a daughter 43, had had frequent epistaxes since childhood and had telangiectases on the face

In cases of recurrent epistaxis or chronic secondary anemia for which no cause is found, hereditary hemorrhagic telangiectasis should be considered and a search made for characteristic lesions in nasal oral and pharyngeal mucous membranes Presence of telangiectases in the skin and a family history of similar lesions or frequent epistaxis complete the diagnosis

[The following articles are concerned with various types of defective coagulation including evidence purporting to demonstrate anticoagulant activity in hemophilic plasma —Eds]

Congenital Afibrinogenemia Report of Case with Review of Literature is presented by J L Henderson G M M Donaldson and Harold Scarborough[9] (Univ of Edinburgh) Total lack of fibrinogen in the blood plasma is rare It may be congenital or acquired when acquired it is sometimes only transitory Congenital afibrinogenemia should be remembered as a possible cause of hemorrhage in congenital bleeders There is still too great a tendency to regard congenital bleeders of the male sex as hemophiliacs without adequate clinical and laboratory investigations to eliminate other possible causes

Boy 11 has been admitted for persistent hemorrhage 11 times Hemorrhage was arrested by transfusion on six occasions and subsided spontaneously on the other five Less severe hemorrhage not necessitating hospitalization occurred many times, the nose was the commonest site Eruption of the first deciduous tooth caused severe hemorrhage and shedding of deciduous teeth was often associated with hemorrhage for two or three days Extensive bruising had always been easily produced Umbilical hemorrhage which began the third day of life (controlled by transfusion after failure of other treatment) was diagnosed as hemorrhagic disease of the new born Diagnosis of hemophilia was made at each subsequent admission until the eighth, at age 7½ when

(9) Qu t J Med 14 101 111 Apr 1 1945

absence of fibrinogen was discovered The parents are first cousins

The disease affects both sexes In this case and six others previously reported five of the patients were boys A hemorrhagic tendency is evident from birth showing that the condition is congenital Consanguinity is a significant feature Parents were first cousins in three of the seven cases Occurrence of a hemorrhagic diathesis was noted in two No fibrinogen could be detected in the blood plasma in any case nor did clotting occur Bleeding time shows wide variation it was increased in four cases normal in two and not recorded in one Intermittent thrombocytopenia was observed in two instances Platelet count was always within normal limits in the other five A low sedimentation rate was demonstrated in both cases in which this test was done

Capillary resistance tests were not mentioned in most cases The positive pressure method (Hess) demonstrated diminished capillary resistance in Macfarlane s case but no abnormality was demonstrated by this method in the authors case According to the method of Scarborough which assesses capillary resistance in terms of the least negative pressure (in millimeters of mercury) required to rupture capillaries in each of three standard areas of skin capillary resistance was always unduly low It is important that although the negative pressure test consistently gave very low values for capillary resistance the positive pressure (tourniquet) test was negative

Expectation of life is short Four patients died in childhood and none of the remaining three had passed beyond this period at the time of report There appears to be great danger of fatal umbilical hemorrhage in early life This occurred in a sister of the authors patient and also in a sister of Macfarlane s patient

Four cases of congenital hypofibrinogenemia have been recorded in adults All had been bleeders most of their lives and there was a family history of hemorrhagic diathesis in three In each instance blood plasma contained only about one twentieth the normal amount of fibrinogen Frequency and severity of hemorrhage are

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(9) Q t J M d. 14 101 111 April 194

absence of fibrinogen was discovered The parents are first cousin

The disease affects both sexes In this case and six others previously reported five of the patients were boys A hemorrhagic tendency is evident from birth showing that the condition is congenital Consanguinity is a significant feature Parents were first cousins in three of the seven cases Occurrence of a hemorrhagic diathesis was noted in two No fibrinogen could be detected in the blood plasma in any case nor did clotting occur Bleeding time shows wide variation it was increased in four cases normal in two and not recorded in one Intermittent thrombocytopenia was observed in two instances Platelet count was always within normal limits in the other five A low sedimentation rate was demonstrated in both cases in which this test was done

Capillary resistance tests were not mentioned in most cases The positive pressure method (Hess) demonstrated diminished capillary resistance in Macfarlane s case but no abnormality was demonstrated by this method in the authors case According to the method of Scarborough which assesses capillary resistance in terms of the least negative pressure (in millimeters of mercury) required to rupture capillaries in each of three standard areas of skin capillary resistance was always unduly low It is important that although the negative pressure test consistently gave very low values for capillary resistance the positive pressure (tourniquet) test was negative

Expectation of life is short Four patients died in childhood and none of the remaining three had passed beyond this period at the time of report There appears to be great danger of fatal umbilical hemorrhage in early life This occurred in a sister of the authors patient and also in a sister of Macfarlane s patient

Four cases of congenital hypofibrinogenemia have been recorded in adults All had been bleeders most of their lives and there was a family history of hemorrhagic diathesis in three In each instance blood plasma contained only about one twentieth the normal amount of fibrinogen Frequency and severity of hemorrhage are

considerably less in congenital hypofibrinogenemia than when there is total absence of fibrinogen There was no record of consanguinity in these cases Clotting time was normal in all four cases in contrast to complete absence of clotting in congenital afibrinogenemia Bleeding time was also normal The positive pressure test (Rumpel Leede) demonstrated diminished capillary resistance in only one of the three cases in which it was done No negative pressure tests were made Blood sedimentation rate was normal in three cases in which it was done Expectation of life apparently is good in congenital hypofibrinogenemia

Schonholzer has suggested that congenital afibrinogenemia and congenital hypofibrinogenemia may be variants of the same hereditary disease and that parents of patients with the former are homozygous, while those of patients with the latter are heterozygous The authors believe that the relationship, if any between the two diseases cannot be clarified until more cases have been investigated

Hemophilia Like Disease in Females Note on Clotting Time of Recalcified Plasma Frederick W Madison and Armand J Quick[1] (Marquette Univ) report a case

Woman 30 had a negative history of hemorrhage Menstrual flow since the last pregnancy had been somewhat greater than previously but was not excessive Ten months before admission there had been a rash around the waist which was thought to be shingles Shortly thereafter extensive ecchymosis developed in the left calf muscles and subsequently in multiple areas many of which showed only moderate swelling and ecchymosis In no instance was trauma responsible She had two severe episodes of hematuria The characteristic deep muscular and subcutaneous hemorrhages continued for six months when the gums bled for a short period and deep hemorrhages seemed to increase in size and frequency There was no known instance in the family for three generations of abnormal tendency to bleed or bruise easily

Physical examination was negative except for marked swelling and tenderness of the left forearm from wrist to elbow and variably sized ecchymotic areas on other extremities Bleeding time clot retraction time prothrombin concentration and platelet count were normal, whereas coagulation time was distinctly de

(1) Am J M Sc 09 443 447 Ap il 1945

layed and the tourniquet test was positive Large amounts of fruit juices cevitamic acid and subsequently hesperidin were prescribed witl out appreciable effect on the tourniquet test Muscular and subcutan ous hemorrhages continued with variable frequency After one month apparent improvement followed and two months after the first examination the tourniquet test was normal Sudde ly a few days later spontaneous hemorrhage ap peared in the base of the tongue and muco a of the pharynx causing difficulty in breathing and swallowing De pite trache otomy oxy_en and artificial respiration the patient died Autopsy findings were completely negative except for extens ve hemor rhag c infiltration of subl ngual submaxillary and laryngeal areas and sli ht tubular degeneration of the kidneys

Laboratory findings in this hemophilia like condition were similar to those of true hereditary hemophilia ex cept for the clotting time of recalcified plasma Oxalated hemophilic plasma subjected to high centrifugation clots significantly slower on recalcification than that obtained by spontaneous sedimentation or slow centrifugation In marked contrast the plasma of this patient failed to show this striking difference due to centrifugation The significance of this test is not yet known but Quick has observed that it has been consistently positive in a small series of hemophilia cases and that it was negative in one other atypical or hemophilia like condition

In 1938 Joules and Macfarlane described a similar case in a woman 56 who developed a hemorrhagic diath esis after extraction of a tooth A similar instance in a woman 33 was described to the authors by Loveman These three cases appear to be identical In each the hem orrhagic condition appeared in a woman with no previ ous attacks of abnormal bleeding or familial history of hemorrhage The clinical picture and type of bleeding simulates hemophilia and is almost certainly due to pro longed coagulation time of the blood The diathesis can be equally as serious as hemophilia and may terminate fatally In Loveman s and the authors cases the hemor rhagic condition began several months after childbirth Significantly menstruation was normal and unaccom panied by excessive bleeding despite a prolonged coagu lation time This seems to indicate that hemostatic control

of menstrual bleeding is not dependent on the coagulation mechanism

Principal differences between this clinical entity, true

DIFFERENTIAL DIAGNOSIS OF HEMOPHILIA AND HEMOPHILIA LIKE DISEASES

	Human Hemophilia	Swine Hemophilia	Hemophilia Like Disease in Women
Heredity	Recessive sex linked	Simple recessive	
Sex	Male	Male and female	Female
Transmission	Female	Male and female	
Time of onset	Infancy	Early	Adult life
Bleeding			
Type	Deep	Deep	Deep
Cause	Traumatic	Traumatic	Spontaneous
Coagulation	Delayed	Delayed	Delayed
Clotting time test of recalcified plasma	Positive	Positive	Negative

B. E. Hall states that he has studied a female patient at Mayo Clinic with a clinical picture similar to that described by the authors

hemophilia and the hemophilia like disease of swine are summarized in the table

Influence of Contacting Surface on Coagulability and Anticephalin Activity of Normal and Hemophilic Plasmas was studied by Leandro M Tocantins[3] (Jefferson Med College) Normal plasma collected with special precautions reduces the clot accelerating action of homologous brain extracts This activity seems to be exerted on the cephalin fraction of the thromboplastic lipoprotein and may properly be designated as anticephalin activity Plasma placed in contact with certain surfaces (e g asbestos clay glass) loses this activity rapidly as its coagulability increases The well known difference between coagulation rates of blood in vessels with walls of varied composition (e g glass and paraffin) appears likewise to be related to anticephalin content of plasma When there is an excess (as in hemophilic plasma), the difference is most pronounced in normal plasma the difference becomes less and it may cease to be evident when anticephalin is reduced or removed by contact with adsorbents

(3) Am J Phys 143 67 76 January 1945

In order of their effectiveness the following materials (10 mg per ml plasma for two hours at 20 C) enhance coagulability of plasma brought into contact with them asbestos fibers infusorial earth kaolin pumice stone filter cell talc glass particles and glass wool Animal charcoal permutit and silica gel seemed less effective and cellophane strips cotton fibers iron aluminum copper and brass shavings have no significant effect Partial immersion of a Pasteur Chamberland filter candle in cell free citrated normal plasma for one hour reduces to one third or less the clotting time and anticephalin activity of the plasma Filtering 10 cc plasma through a Berkefeld V filter over 40 seconds removes some of its prothrombin and so alters the plasma that on addition of cephalin it clots faster than unfiltered plasma with normal prothrombin content The amount of calcium required for optimal recalcification is not changed after contact of plasma with asbestos indicating that there has been no loss in citrate Plasmas exposed to adsorbents are nevertheless quite unstable After standing one to two hours even at 5 C plasmas filtered through Berkefeld candles or Seitz pads begin to clot spontaneously Spontaneous conversion to thrombin of purified prothrombin solutions even in the absence of calcium may result from loss of protection afforded by anticephalin against the effects of contact

Unlike normal and hemophilic plasma dilution of adsorbed plasma prolongs its clotting time from the outset and does not alter its behavior in the two types of vessel Adsorbed plasma clots at approximately the same rate in glass or lusteroid tubes and effect of incubation with cephalin is not striking Since reduction of anticephalin activity by diluting plasma or exposing it to adsorbents is manifested by decreases in difference between clotting time in glass and lusteroid vessels extent of this difference may give an approximate measure of this activity In general coagulation of plasma proceeds at a slower rate in paraffin collodion lusteroid or acryloid tubes than in glass

DISEASES OF THE KIDNEY

The articles in this section deal with the physiology patholo- and clinical aspects of renal disease —Eds

PHYSIOLOGY

Renal Regulation of Acid Base Balance with Special Reference to Mechanism for Acidifying Urine Large quantities of acid are continuously produced in the body by metabolism of various foodstuffs yet in health the hydrogen ion concentration of body fluids is remarkably constant This regulation of balance between acid and base constituents depends on both respiratory and renal homeostatic mechanisms Quantitatively the rate of production of carbonic acid amounting to about 20 mols per day far exceeds that of other metabolic acids but because of volatility of its anhydride, carbon dioxide carbonic acid is readily and rapidly eliminated by the lungs Less than one one hundredth of this quantity of phosphoric and sulfuric acid is produced daily yet their excretion effected largely by the kidneys, is in some ways a greater problem than excretion of the much larger quantities of carbonic acid Rarely does any disease process lead to disturbance of acid base balance because it interferes with elimination of carbon dioxide in the lungs In contrast at least two diseases severe uncontrolled diabetes and chronic diffuse glomerulonephritis lead to disturbances of acid base balance because they interfere with adequate elimination of acid by the kidneys

Robert F Pitts[4] (Cornell Univ) presents a new concept of the nature of the renal cellular mechanism for acidifying the urine (Fig 73) A single cell from that part of the distal segment of the renal tubule concerned with acidification of the urine is illustrated On the left is the lumenal border of the cell in contact with the tubu

(4) S i n 10 49 54 J ly 0 81 85 July 27 194

lar urine On the right is that border of the cell which is in diffusion equilibrium with renal tubular blood Carbon dioxide is produced within the tubular cell by oxidative metabolic processes and may also diffuse into the cell from the peritubular blood This carbon dioxide is hydrated to form carbonic acid The enzyme carbonic anhydrase serves to increase catalytically the rate of production of carbonic acid but is not essential for hydration Carbonic acid dissociates within the cell to form hydrogen and bicarbonate ions the hydrogen ions are exchanged for sodium ions in the tubular lumen and

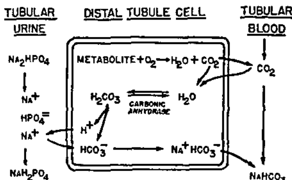


FIG 73—D g m f t f enal ll la m h i m f a d fyi g (F m P tt R F a d A d R S Am J Phy ol 144 39 1945)

sodium ions accompanied by an equivalent number of bicarbonate ions are reabsorbed into the tubular blood While details of this scheme are largely hypothetical it explains adequately the known facts concerning excretion of titratable acid namely that hydrogen ions are added to the tubular urine by renal tubular cells that an equivalent amount of base is retained in the body and that the enzyme carbonic anhydrase is in some way concerned in the process

The quantity of base saved or conversely the quantity of free titratable acid excreted by this mechanism is determined by three major factors (1) quantity of buffer available for the kidney to operate on (2) strength of

the buffer i e, how strongly it resists giving up its sodium ions in exchange for hydrogen ions and (3) severity of the acidosis, which is a measure of the need of the body for conservation of its basic constituents

Under normal conditions capacity of the kidney to exchange hydrogen ions for sodium ions is sufficient to permit excretion of the fixed metabolic acids without depletion of body stores of fixed base In diabetes excessive production of metabolic acid so overwhelms the renal mechanism that it is incapable of full compensation and progressive acidosis develops Two of the buffer acids formed in this disease beta hydroxybutyric and acetoacetic acids are too strong for the kidney to operate on effectively In nephritis the mass of functional renal tissue is reduced Therefore each remaining unit must carry more than its normal share of the burden of acid elimination Furthermore, the disease probably has reduced the capacity of these remaining units to excrete acid as compared with the capacity of normal units Perhaps it has done so by restricting the chemical work which renal tubular cells can do or perhaps the process has specifically reduced the cellular content of the vital enzyme carbonic anhydrase

Blood Plasma Volume and Serum Protein Studies during Diuresis George M Decherd, D Bailey Calvin and George R Herrmann[5] (Univ of Texas) studied changes in plasma volume during diuresis induced by salyrgan, aminophylline mercupurin and digoxin These changes do not appear to cause the diuresis but simply reflect the balance of fluid mobilization from tissues into the circulating plasma and fluid loss from plasma into the tissue spaces or by renal excretion

Diuresis after administration of digoxin is probably due to improvement of myocardial function by the drug restoration of cardiac compensation reduction of venous pressure and secondary increase in rate of urinary flow The site of action that leads to diuresis is on the heart muscle The mercurial and xanthine diuretics act on both

(5) Texas R p Bl 1 & M d ? 47 60 1944

renal excretory units and tissues or blood stream That mercupurin resembles salyrgan rather than aminophylline in its effect on renal clearances led to the suggestion that the drug be fortified by additional xanthine When judged by changes in blood volume the mercupurin effect is predominantly that of the xanthine aminophylline Variation in the type of action at renal and extrarenal loci may further clarify the clinical efficacy of mercupurin

With the diuretics studied changes in blood plasma protein concentration depend largely on shifts in plasma volume and occur in the direction required for approximate maintenance of colloid osmotic pressure

Incidence Causes and Intermittency of Proteinuria in Young Men Irving J Wolman[6] (U S Pub Health Service) reports that urine examinations of 22 000 presumably healthy American men entering the U S Maritime Service revealed proteinuria in 420 (1 9 per cent) In most instances representing 1 7 per cent of the original group proteinuria was intermittent or orthostatic with the highest incidence at age 16 The remaining men in the series had either continuous proteinuria due to no elicitable cause mild unsuspected nephritis or urologic disease

Intermittent proteinuria in young persons is a harmless benign condition provided there are no associated clinical or urinary changes In study of disturbances accompanied by proteinuria concentration of protein in random specimens of urine is not helpful as a diagnostic guide In random analysis of single specimens nephritis will usually reveal itself but more cases of urologic or benign intermittent proteinuria will be missed than discovered

(6) Am J M S 210 86-100 J ly 1945

Pathologic Basis for Clinical Manifestations of Nephritis James P Simonds[7] (Chicago) reports six illustrative cases Each kidney is composed of approximately 1 000 000 units each essentially complete in itself, with characteristic anatomic structure, functions and its own blood supply The glomeruli probably furnish a filtrate consisting of a solution not only of waste products but of all crystalloidal substances in plasma The proximal convoluted tubules by selective reabsorption, return to the blood substances which the body can ill afford to lose Henle s loop reabsorbs water and concentrates urine The distal convoluted tubules alter the reaction of the urine thus conserving alkali reserve and maintaining acid base balance of the body The parts of each unit are interrelated through their common blood supply, consisting of two systems of capillaries glomerular and peritubular Interference with blood supply of the glomeruli also affects that of the tubules Hence in disease of the kidneys the unit suffers as a whole

The two chief types of nonsuppurative renal disease are glomerulonephritis (Bright s disease) and vascular nephropathy although differing greatly in basic pathology both interfere with circulation through the kidneys Vascular nephropathy is associated with hypertension, and death usually results from congestive heart failure or cerebral hemorrhage Glomerulonephritis, because changes in the glomeruli reduce filtration usually ends in uremia However, patients with vascular nephropathy occasionally die of renal insufficiency, while those with glomerulonephritis sometimes die of congestive heart failure Either type may run an atypical course with clinical manifestations of the other

In early glomerulonephritis inflammatory reactions in the glomeruli may be exudative or proliferative The exudative form because of free drainage through the tubules usually heals without serious consequences The

(7) Illinois M J 87 1 6 13 March 1945

proliferative lesion unless for some unknown reason the process ends spontaneously progresses to a fatal termina tion

Edema a frequent complication of glomeruloneph ritis may occur in three different stages of the disease with a different mechanism in each In acute glomerulo nephritis the systemic capillaries are injured their walls become more permeable and serum albumin escapes into the tissues where it holds water thus giving rise to edema. [But see a contrary view expressed in following article —Eds] In the nephrotic stage serum proteins be come depleted as a result of loss of serum albumin in the urine when the quantity of serum albumin in the plasma falls below a critical level normal balance between hydro static pressure of the blood and osmotic pressure of plasma proteins is so disturbed that more water leaves the capillaries than returns to them and edema of tissues results Later the nephrotic edema disappears spontane ously This is not a sign of improvement because it is due to progressive destruction of glomeruli In the very late stages of chronic glomerulonephritis hypertension develops and cardiac edema may follow onset of con gestive heart failure The edema of vascular nephropathy is due to congestive heart failure

Protein Content of Edema Fluid in Patients with Acute Glomerulonephritis was determined by James V Warren and Eugene A Stead Jr[8] (Emory Univ) in 10 cases (see Table) Average values do not differ signifi cantly from those for edema fluid of patients with con gestive heart failure studied by similar methods

Evidence indicates that edema in acute nephritis is caused by water and salt retention secondary to a dis turbance in renal function and not by diffuse capillary damage throughout the body The method of study used is not suitable for determining whether retention of salt and water results from the pathologic process occurring in the kidney or from heart failure as suggested by LaDue Extensive pathologic changes seen in the kidney

(8) Am J M S 208 618 6 2 N ember 1944

in acute glomerulonephritis support the view that the altered renal function is caused by these pathologic

SUBCUTANEOUS EDEMA FLUID IN 10 PATIENTS WITH ACUTE GLOMERULONEPHRITIS

Case	Blood Serum		Protein Content of Edema Fluid	
	Nonprotein Nitrogen Mg per 100 Cc	Total Protein Gm per 100 Cc	Leg Gm %	S[illegible]l Region Gm %
1	41	5 8	0 4	
2	33	6 5	1 0–1 1	
3	63	6 1	0 2–0 3	0 5–0 [illegible]
4	198	6 [illegible]	0 1–0 3	
5	34	5 8	—	0 8
6	—	6 5	—	1 0
7	54	5 8	0 1	
8	[illegible]4	5 2	0 1–0 2	
9	—	6 4	—	0 9–1 0
10	50	4 9	0 3	
Av	—	5 9	0 4	0 8

changes rather than by altered renal physiology because of heart failure

CLINICAL DESCRIPTION

Chronic Glomerulonephritis and Nephrotic Syndrome Follow Up Investigation of Patients Treated with Acacia is presented by Raymond E Smalley and Melvin W Binger[9] (Mayo Clinic) On admission the 109 patients selected for study had glomerulonephritis and the nephrotic syndrome with extensive and resistant edema they were treated with injections of acacia in 1937–43 By nephrotic syndrome is meant the clinical state characterized by albuminuria edema and a decreased serum albumin concentration In addition, blood cholesterol concentration usually is elevated, and frequently basal metabolic rate is lowered Of the 109 patients 72 were alive and 25 dead at the time of follow up no response was received from 12 Of the 72 patients 27 were over 40 at the time of follow up Most patients were

(9) J A M A 1 6 53 535 Oct 28 1944

in their teens when symptoms appeared and the next largest number were in the third decade Three were under 10 and 2 were over 68

Treatment is directed toward removing edema and restoring normal concentration of serum protein Sodium intake was restricted and serum protein concentration protected by high protein intake Vitamins and iron may be used Administration of acacia is indicated when renal function is good serum protein concentration is low and edema does not respond readily to treatment The usual total dose is 90 Gm i e a 6 per cent solution of pure acacia in 1 500 cc of 0 06 per cent solution of sodium chloride One third this quantity is given in each of three intra venous injections administered usually on alternate days In the average case in which fluid intake is controlled this quantity will give a concentration of approximately 2 Gm acacia per 100 cc blood serum If it fails to do so or if clinical edema is still present further injection can be given Mercurial diuretics may be more effective after administration of acacia than before The acacia is grad ually eliminated from the blood One year after admin istration average concentration is 100 mg per 100 cc serum In one patient re examined six years after her last injection the concentration of acacia in the blood serum was 10 mg per 100 cc

Twenty of the 25 patients who were dead at the time of follow up had lost their edema when hospitalized under treatment which included administration of aca cia Twelve lived two years or longer and five four years or longer Listed causes of death were further manifes tations of chronic Bright s disease such as uremia hyper tension and cardiac failure in most also acute appendi citis mastoiditis pancreatitis septicemia and old age were reported

Of the 72 living patients 49 were doing a full day s work 2 were only slightly handicapped 19 were work ing part time at least half a day and 2 were bed pa tients One of the last was a man aged 74

Twelve patients had reactions during acacia adminis-

tration consisting of coldness of the extremities, flushing of the face chill nausea vomiting, dyspnea and urticaria Two of these 12 had reactions two or three times but all patients were able to complete the necessary injections including one with proved allergy Plasma fibrinogen remained normal and no instances of bleeding tendency developed

Using microscopic evidence of erythrocyturia leukocyturia and cylindruria and presence of albuminuria as criteria 20 of 38 patients re examined gave evidence of improvement in urinary findings 11 showed some improvement 5 showed definite improvement and the urine of 4 was normal

Other laboratory examinations in these patients and follow up reports on the others indicate that many patients who had resistant nephrotic edema and were treated successfully with acacia and other procedures have been able to maintain a more nearly normal economic and social existence than had been possible before treatment There was no evidence that acacia was harmful

Use of Posterior Pituitary Extract in Tests of Urinary Concentration R D Taylor (Cleveland) James D Peirce (Indianapolis) and Irvine H Page[1] (Cleveland) compared the results of these tests with those of the Addis test which necessitates water deprivation for 24 hours, in 33 normal and 65 abnormal persons The latter group consisted of persons with essential or malignant hypertension chronic glomerular nephritis or chronic pyelonephritis Pituitrin pitre sin in oil short periods of dehydration and combinations of these were tried in the hope that a less disagreeable test might be devised None of these procedures attained the mean concentration of 1 030 recorded after 24 hours dehydration in normal subjects Range of variation was 1 016–1 033 as compared with 1 026–1 032 with the Addis test Similar variability was observed in abnormal subjects receiving pituitary extracts

(1) Am J M Sc 09 35 740 February 1943

The authors conclude that substitutes for the Addis test which do not approximate the ceiling of specific gravity are not entirely acceptable in clinical practice

Prognostic Significance of Elevated Blood Creatinine and its value as compared with other renal function tests are discussed by Victor C Myers (Western Reserve Univ) Apparently the Van Slyke urea clearance test gives the most reliable measure of renal insufficiency especially in early renal disease When definite impairment in renal function has been established blood urea nitrogen should also be considered since this is available from data required for calculation of urea clearance When there is definite elevation of blood urea nitrogen creatinine level should also be determined Practical experience conclusively demonstrates the superiority of blood creatinine over urea nitrogen determinations as a prognostic sign in patients with severely impaired renal function While essentially the same prognosis might be given in many cases on the basis of figures for urea nitrogen alone there are instances in which creatinine may be elevated above the critical level without presence of correspondingly high values for urea nitrogen Theoretically this finding would seem logical since creatinine is more readily eliminated than urea is excreted by the human kidney somewhat differently than urea in that the tubules participate and is almost entirely endogenous whereas urea under ordinary conditions of diet is largely exogenous

The urea clearance test is also of good prognostic value but with marked retention the blood creatinine test shows greater changes and therefore is more significant While the phenolsulfonphthalein test has proved valuable as a renal function test the dye output is so low with severe renal impairment as to reflect changes at this stage inadequately Rise in level of inorganic phosphorus in advanced renal disease is an infallible sign of marked impairment in renal function However it comes a little later than retention of creatinine The

(2) J L b & Cl n Med 29 1001 1018 Oct be 1944

value of determination of indican, the diazo reaction and the xanthoproteic reaction has been demonstrated but these tests do not have greater reliability than the blood creatinine test which is a simpler procedure

Effect of Pregnancy on Renal Function in Women with Pre Existing Essential Hypertension and with Chronic Diffuse Glomerulonephritis Irwin Wellen, Catherine A Welsh and Howard C Taylor Jr[3] (New York Univ) report a study involving application of renal clearance methods to six patients with essential hypertension and to two with chronic glomerulonephritis during their pregnancies and repeatedly during one to four years after delivery Observations were also made on three patients before conception

During seven pregnancies in the six patients with essential hypertension there was no consistent rise in blood pressure variations from week to week being no *greater than before conception or after delivery,* and there were no other signs of superimposed toxemia The seven pregnancies resulted in birth of healthy normal infants at term with two exceptions and these terminated in birth of stillborn prematures After labor blood pressure elevation persisted but there has been no evidence in postpartum observation of one to four years that pregnancy accelerated or otherwise altered the course of hypertension Inulin or mannitol clearance was within normal limits in all cases before during and after pregnancy Diodrast Tm as studied in five patients was normal throughout Effective renal blood flow, as measured by diodrast clearance in five pregnancies and indicated by phenol red clearance in the other two, was subject to significant variations Before conception *the figure for* renal blood flow tended to be low in three patients in each, diodrast clearance rose during pregnancy After all five pregnancies studied by diodrast clearance blood flow was somewhat below normal In two additional pregnancies studied by phenol red clearance there was also a higher figure during pregnancy than after delivery

(3) J Cl n In est g t a 23 742 749 September

In three of the seven pregnancies studied renal blood flow had fallen somewhat in the last observation before delivery so that had these studies been limited to the last three weeks of pregnancy increase in blood flow during pregnancy might have been overlooked The filtration fraction (C_{IN}/C_P) and the inulin/phenol red clearance ratio are affected by these changes in renal blood flow Generally these ratios were high before conception and after delivery but approached normal during pregnancy Decrease in filtration fraction during pregnancy in hypertensive women may be attributed to diminished tone of the efferent arteriole from the glomerulus

The two patients with chronic diffuse glomerulonephritis were delivered at term of normal children without increase of hypertension or proteinuria After 28 and 16 months both continued to show evidence of active glomerulonephritis with hypertension proteinuria and hematuria but in neither was there evidence of significant progression of the renal lesion resulting from pregnancy In contrast to the observations in patients with essential hypertension in this disease pregnancy apparently had no effect on renal blood flow This might be due to the more permanent character of changes causing disturbances in renal function with chronic nephritis

Failure to find signs of deterioration in renal function after pregnancy in women with essential hypertension or chronic glomerulonephritis has practical significance It is inferred since an attack of specific toxemia of pregnancy may have chronic vascular disease as a sequel and since superimposed toxemia may occur in hypertensive patients that an attack of toxemia in a patient already suffering from essential hypertension or chronic glomerulonephritis will be detrimental However it is also evident that patients with these diseases may go through pregnancy without added complications and with no permanent effects on renal function

Renal Failure Simulating Adrenocortical Insufficiency Several authors have shown that the hormone of the adrenal cortex aids in maintenance of a normal

value of determination of indican the diazo reaction and the xanthoproteic reaction has been demonstrated but these tests do not have greater reliability than the blood creatinine test, which is a simpler procedure

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(3) J Cl In est gat n 23 42 749 S ptembe r

cause of the physiologic implications but because therapy directed toward correcting the metabolic disturbances resulted in rehabilitation for a life of economic usefulness for periods of two to four years

Both patients a man and a woman aged 1 were without clinical evidence of previous renal impairment and both were admitted in collapse with hemoconcentration dehydration and hypochloremia Both were treated initially with sodium chloride and glucose solutions as well as adrenocortical hormone Dramatic improvement followed However following restoration of plasma volume and blood pressure azotemia persisted and renal function tests revealed persistent high grade renal insufficiency Ultimately it was shown conclusively that whereas sodium chloride and water were life saving adrenocortical hormone preparations were of no value. Clinical improvement accompanied adequate sodium chloride and sodium bicarbonate therapy However moderate hypertension edema and moderate proteinuria developed terminally in both patients

The authors believe that this clinical syndrome is probably not associated with a typical pathologic lesion in the kidney but rather occurs late in the course of insidious progressive renal disease Slow progression and absence of involvement of all nephrons at any one time permit considerable adaptation to fairly high grade renal insufficiency The renal damage is associated with extensive scarring a few remaining hypertrophied glomeruli and dilated tubules Less severe loss of sodium and chloride is not infrequently observed in patients with chronic nephritis and striking benefit may follow judicious use of small quantities of supplementary sodium chloride and sodium bicarbonate under such circumstances

For convenience and for its therapeutic implication patients with chronic renal disease presenting evident signs and symptoms of sodium and chloride depletion may be said to be suffering from salt losing nephritis'

Intercapillary Glomerulosclerosis Association of intercapillary glomerulosclerosis with a distinct clinical syndrome was first pointed out by Kimmelstiel and Wilson in 1936 The characteristic symptom complex consisted of a history of diabetes mellitus usually of long standing widespread edema of renal origin and pro-

state of hydration by increasing the renal tubular reabsorption of sodium chloride and water Theoretically one might expect to encounter at some time a type of renal tubular damage or incapacity that would prevent the adrenocortical hormone from exerting its usual effect on tubular reabsorption of sodium and chloride (Fig 74) Under these circumstances a clinical picture simulating the electrolyte disturbance seen in Addison s disease

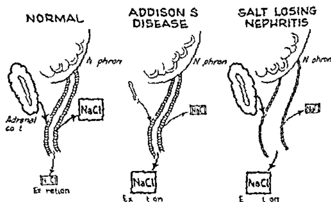


Fig 74

might be presented by a patient with intact, normal adrenal glands

Hypochloremia and dehydration have been described in patients with renal disease and occurrence of this phenomenon in patients with uremia without edema is well known George W Thorn, George F Koepf and Marshall Clinton, Jr [4] believe however, that occurrence in patients with chronic nephritis and normal adrenal glands of a shock-like state indistinguishable from that of acute adrenal insufficiency has not been reported They report on two patients who on admission were thought to have acute adrenal insufficiency Subsequent studies over two to four years including autopsy proved that metabolic changes followed renal rather than adrenal disease These cases are interesting not only be

(4) New England J Med 231 76 85 July 20 1944

focal fibrosis of the glomerular tuft and a small typical circular hyaline mass

This stage of development has not been described in other reports Its recognition and inclusion account partly for the high incidence of intercapillary glomerulosclerosis in this series This mild degree of glomerular involvement occurred in 24 1 per cent of 79 diabetic patients with intercapillary glomerulosclerosis In these patients nearly all glomeruli in both kidneys showed an



Fig 75 —H m t xyl n eo edu ed f m × 1

approximately equal degree of focal fibrosis but no characteristic spherical hyaline masses In absence of diabetes fibrosis also occurs in some glomeruli of kidneys with arterial and arteriolar nephrosclerosis chronic pyelonephritis or chronic glomerulonephritis In these however absence of typical intercapillary glomerulosclerosis can be excluded by variation in degree of glomerular fibrosis presence of many normal glomeruli occurrence of adhesions between glomerular tufts and capsules of Bowman and a variable degree of atrophy of tufts All stages of intercapillary glomerulosclerosis are

nounced albuminuria Frequently hypertension and renal insufficiency were also present The renal lesion was characterized by focal hyalinization of the intercapillary connective tissue *and was named intercapillary* glomerulosclerosis

T C Laipply, O Eitzen and F R Dutra[5] (Western Reserve Univ) reviewed clinical records, autopsy protocols and microscopic sections of 332 patients to determine incidence of intercapillary glomerulosclerosis and to correlate its occurrence and development with distinctive clinical manifestations Intercapillary glomerulosclerosis was common in diabetic (63 7 per cent of 124) and un*common in nondiabetic patients typical glomer*ular lesions occurring in only 5 cases in which a history of diabetes could not be established In one instance there was associated moderate chronic pyelonephritis, in another marked arterial and arteriolar nephrosclerosis, in one subacute glomerulonephritis and in two chronic glomerulonephritis One patient with chronic glomerulonephritis had glycosuria a few months before death, but a diagnosis of diabetes could not be established from clinical data

The typical lesion of intercapillary glomerulosclerosis is usually spherical and occasionally oval It varies from 20 to 110 microns in maximal diameter and consists of faintly acidophilic acellular hyalinized tissue At the periphery there are usually one or more concentric layers of flattened cells presumably endothelial Involved glomeruli sometimes are small but more frequently are of normal or larger size

In kidneys of diabetic patients with typical spherical lesions there is also focal fibrosis of nearly all glomeruli Association of these glomerular changes led to recognition of a lesser degree of development of the lesion in which there is focal fibrosis of most glomeruli without spherical hyaline masses In many cases there are definite transitions from this focal glomerular fibrosis and the circumscribed hyaline masses Figure 75 shows advanced

(5) Ar h I t Med 74 354 364 N embe 1944

Indirect evidence sug_gests that the hypoptoteinemia of Bright s disease whether it occurs during chronic glomerulonephritis or in malignant hypertension with renal failure apparently serves as a means of maintain ing glomerular filtration when in the absence of hypo proteinemia the proportion of water filtered through the glomeruli would be grossly deficient or nil

Nephrocalcinosis Associated with Hyperchloremia and Low Plasma Bicarbonate G H Baines J A Barclay and W T Cooke[7] (Birmingham Univ) report a case

Woman ?9 had polyuria extensi e bilateral renal stone rai ed serum chlorides low plasma bicarbonate and relatively fixed specific gravity and pH of the urine On a sodium citrate citric acid mixture she regained good health and blood values became approximately normal Kidney function remained unchange l

The striking feature of the gross disturbance of electrolyte balance was increase of chlorides at the expense of serum b car bonate There are three theoretical explanations for this increase (1) alter it on of inte tinal habit lead ng to increase l ab orption of chloride or loss of base without accompany ng chlor de (2) hyperpnea and (3) relative loss of renal ability to excrete chlo rides Since the pati nt never had an intestinal upset or hype pnea the first two could be excluded She improved w th provision of extra base hence it was concluded that the tubules were in capable of forming sufficient ammonia to allow excretion of acid radicals without excessive loss of vital basic elements With pro vision of extra base necess ty for ra sed serum [illegible] to main ta n osmotic pressure of the plasma disappe[illegible] s [illegible] th consequent return of p ote n values to normal It was not obvious however whether the tubular dysfunction was primary or secon lary to endocr ne factors metabolic errors or local inflammatory lesions such as nephritis Existence of polyuria for at least 20 year seemed to rule out a nephrit c les on

The pat ent died five years after she was first seen death ap parently be ng p ec pitated by a seve e reaction to sulfathiazole Preliminary h stopathologic examinat on of the k dneys showed calc fication in the pyramids and pelvis, but ne l [illegible]ible amounts n tubules and tissues The tubules showed extensive vacuolation and altered ep thelium Occasional glomeruli were atrophied There was no evidence of pr mary chron c vascular d sease or glomerulonephr t s These findings apparently support the clinical opinion of tubula dysfunction

Four similar cases arising before puberty have been

(7) Q rt J Med 14 113 1 3 Ap l 1945

readily distinguished from glomerular lesions occurring in disseminated lupus erythematosus

Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension Renal Aspects A C Corcoran and Irvine H Page[6] state that it is difficult to distinguish between pre uremic renal failure due to terminal glomerulonephritis and that due to malignant hypertension Because the differentiation is left to the pathologist the concept has arisen that it is not clinically possible to establish the diagnosis by study of renal function The authors prove that this is not true by studies on two groups of 10 patients each with terminal glomerulonephritis and malignant hypertension with renal failure, respectively selected because they presented the lowest levels of renal function observed in two larger series of patients in the absence of the clinical syndrome of uremia

Terminal glomerulonephritis is distinguished by a lower rate of glomerular filtration and tubular secretory capacity for diodrast and usually a higher rate of proteinuria than appear in malignant hypertension with renal failure Despite the lower level of renal excretory function patients with terminal glomerulonephritis survive more than four times as long as those with malignant hypertension with renal failure Changes of renal function usually demonstrable in the patient with terminal nephritis accord with structural changes in the kidneys of such patients in that they indicate lesions that are glomerular and capillary in locus associated with great parenchymal destruction and fibrous replacement and suggest frequent occurrence of large inequalities of function in remaining nephrons

In malignant hypertensives with renal failure, intraglomerular hydrostatic pressure does not seem to be increased or is even low apparently as the result of severe arteriolar disease proximal to the glomerulus In some patients, intraglomerular hydrostatic pressure does not seem to be increased or is even low

(6) Ann Int Med 1 747 764 N vember 1944

of the blood It is usually manifested by presence of protein casts or cellular elements in urine and by impaired performance of standardized tests of renal function

Principal causes of kidney disease are grouped as follows kidney infections—pyelonephritis pyonephrosis cortical abscesses and perinephric inflammation "allergic disorders—acute and chronic glomerulonephritis (including the nephrotic syndrome) disseminated lupus erythematosus and polyarteritis disturbances in renal circulation—arteriolar nephrosclerosis heart failure and arterial and venous obstruction renal injury from chemical and metabolic agents e g mercury bismuth sulfonamides and gout congenital or acquired malformations —hypoplasia polycystic disease tumors and aberrant vessels

Recognition of kidney infections and institution of appropriate medical and surgical measures may prevent progressive destruction of kidney substance in many patients Use of sulfonamides penicillin and mandelic acid represents a great advance in specific therapy

There is no specific therapy for acute glomerulonephritis Fortunately over 85 per cent of patients with this disease recover and recoveries may be increased appreciably by intelligent and diligent medical care Some evidence suggests that patients who continue to have positive throat cultures for beta hemolytic streptococci are benefited by sulfonamides

Renal insufficiency resulting from vascular disease still presents a field for therapeutic progress Present therapy is limited to treatment of congestive heart failure and attempts to lower blood pressure by medical and surgical methods

Widespread use of chemotherapeutic agents undoubtedly will increase occurrence of renal disease hence prophylaxis is important Incidence of renal insufficiency can be greatly reduced if precautions are taken to insure adequate urine volume

In hypoplasia and cystic disease of the kidney little can be done other than to prevent secondary infection

reported Butler Wilson and Farber in 1936 reported the case of a boy, 10 characterized by persistent dehydration without excessive diarrhea and vomiting and with adequate food salt and water intake, sustained elevation of serum chloride, reduction of serum bicarbonate, advanced rickets and bilateral renal stones, but with no hyperpnea In 1940, Albright and his co workers reported the case of a girl, 13, with persistent rickets and dwarfism, massive calcium deposits in the kidney pyramids hyperchloremia and low level of serum bicarbonate After extensive metabolic studies, it was concluded that the syndrome was a renal tubular disorder with inability to secrete ammonia or to excrete an acid urine shortage of base with which to excrete mineral acids especially chloride radicals, increased calcium loss in the urine acting as a base, secondary hyperathyroidism to meet the tendency of low serum calcium, hypophosphatemia and low phosphorus rickets Boyd and Stearns (1941) reported the case of a girl 11 with essentially similar metabolic findings She died unexpectedly and autopsy showed only slight calcium deposits in the pyramids while the tubules were essentially normal although convoluted tubules were considerably dilated Findings in this case suggested that nephrocalcinosis was not an essential part of the syndrome Boyd and Stearns postulated that the cause was a "perversion of the whole electrolytic system rather than a primary tubular dysfunction" Rule and Grollman (1941) described a case in which the patient a girl suffered from rickets and spontaneous fractures since age 15 months and when first seen at age 15 years was unable to walk Investigations showed multiple renal calculi low plasma phosphorus hyperchloremia low serum bicarbonate and relatively fixed specific gravity of the urine

Suggestions for Treatment of Kidney Disease are outlined by George W Thorn and Frank H Tyler[8] (Harvard Univ) Renal malfunction is characterized by excessive excretion or retention of normal constituents

(8) M Clin North Amer 28 1173 1188 Septem

OF KIDNEY DISEASE

AZOTEMI		E MA AND A O MI		
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1 Gm /kg da ly	1 Gm /kg d ly	1 Gm /kg d l	1 Gm /kg d l	
No t i ti 1–3 G l i y supplem nt§	N r t l t	S lt f	S lt f	
Alk l e 3–6 Gm NaHCO d ly	Alk l 3–6 Gm N HCO d ly	Alk l	Alk l n	
		1 0 Gm I V b i d	1 5 Gm I V b i d	
1 000 5% I V d ly 3–7 days	50 0% I V d ly 3 7 d y			S e f t t ¶
				D gital at ‡
		0 1 Gm I V b d	0 1 Gm I V b i d	0 1 Gm I V b d
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D et	P te n	– 3 Gm / kg d ly	1 – 2 G /kg d ily		1 Gm /kg da ly
	N Cl	Salt f ee	Salt free		No estric t n 1–3 Gn da ly s pple me t§
	Ash	Acid	Ac d		Alkal e
D u et cs	Pla ma alb m	25–50 Gm I V d ly	10–15 Gm I V b d.		
	Urea†	30–60 Gm da ly	30–60 Gm da ly	30 Gm daily	
	Glu				1 000 cc 5% I V d ly 3–7 d y
	D g t l			Dig t liz t n‡	
	Am phyll n			0 1 Gm I V b d	
Special Con ider t on		In pres n e of m a wh l bl od t ansfu s d t d	I pre en e of nau a d omt ng gl solu tion 500 cc 10% I V q 6–8 h albu min o pl ma 8–10 Gm I V q 6–8 hr may be subst t ted for abo	Ox ge P racen t Fl ls a d p l e l t o n s sh ld t be gi e ntr ve ously	In p e c f na sea d v mt ng gl c se solu t on 3 000 c 10% I V sod m hlo le 500 0 85% I V daily may be b tit ted f r abo

The prod cts of pla ma fra t tion u d were devel ped f m blo d c llect d by the Ame can Red C by th D p rtm t of Phy l Chem istry H ard Un e ty under c nt t, mm d d ly the Comm ttee on M d l R ar h, betwe n th Offic of Sc t fic R ear h a d Develop m nt and Ha d U e ty

† U a may be gi n i fru t jui e If a orexi or n usea curs d s hould be reduced o d scont ued

azotemia Agents should be used which act by increasing plasma volume and renal circulation i e protein solutions intravenously glucose solutions intravenously urea and possibly xanthine derivatives Presence of circulatory failure is a contraindication to use of substances which depend for their action on a relatively large increase in plasma volume

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SPECIAL VARIETIES OF RENAL DISEASE

Mechanism of Renal Complications in Sulfonamide Therapy is discussed by Edwin L Prien[9] (Brookline Mass) The usual mechanism that produces renal complications is obstruction of urinary channels by insoluble concretions principally acetyl derivatives of the drugs Less frequently a toxic injury of the tubules independent of concretions produces anuria and uremia In such cases the only lesion in the urinary tract is focal necrosis of the kidney tubules

Prien reports two cases of the latter type due to sulfathiazole In a man 39 treated for pneumonia and a woman 47 treated for acute pharyngitis no obstructing concretions were revealed in the ureters or kidney pelves by cystoscopy and pyelography Renal decapsulation was done and cortical biopsy specimens taken No crystals or concretions were found in kidney tissue The first patient died The other recovered rapidly apparently as a result of decapsulation Autopsy in the fatal case revealed no crystals or concretions in the entire urinary tract including the kidney tubules A rigorous technic precluding loss of drug crystals was used in preparation of tissues

The most important factor in causation of renal complications is a low urinary output Development of obstructing concretions depends on the hydrodynamics of the urinary tract and the affinity of crystals for each other Crystals of the sulfonamides first form in the convoluted tubules where reabsorption of water occurs

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(9) N w E gl d J M d 3 63 68 J n 18 1945

In presence of renal stasis resulting from calculus aberrant vessel or tumor, surgery may improve kidney function or prevent further damage

Elimination of the agent responsible for renal damage is not possible in most patients with kidney disease Hence treatment must be concerned largely with preservation of nephrons and prevention of development of gross chemical and metabolic abnormalities A useful life, including moderate activity, may be carried on for many years despite the reduced functioning kidney mass particularly in patients with renal insufficiency without hypertension

Treatment resolves itself into supplying proper fluid intake, attention to diet and administration of diuretics (see Table) In absence of circulatory failure, water will not be retained in significant quantity without concomitant retention of sodium, hence in patients with "renal edema there is little justification for restriction of fluids on a salt free regimen A large urine volume is advantageous in presence of azotemia Patients with nephritis should be provided with basic dietary requirements necessary for health water sufficient to provide a urine volume large enough to permit excretion of metabolic end products, calories sufficient to maintain weight protein sufficient to meet body needs (1 Gm per kg daily for adults) and to compensate for abnormal losses in urine, essential minerals and vitamins In absence of azotemia high protein diets are indicated, i e 2–3 Gm per kg body weight per day to provide (1) improved nitrogen balance, (2) increased urea excretion (diuretic) (3) increased renal blood flow and (4) acid ash (diuretic) In presence of azotemia protein intake may be restricted to the basic requirement of 1 Gm per kg Patients with edema should be given a salt free diet Those with azotemia without edema are often benefited by administration of supplementary sodium chloride, 3–5 Gm daily

There are two indications for increasing urine output in patients with renal malfunction (1) edema and (2)

similar but in these cases there was no evidence of pigment in the first convoluted tubules or changes in any of the glomeruli

German journals from World War I carried incomplete clinical records of renal failure after various injuries Cases have been reported during World War II under crush syndrome in which the clinical picture and postmortem findings in the kidneys are comparable to those in the present cases Similar changes are sometimes found in cases of injury without crushing including head injuries and also in association with blackwater fever pyloric stenosis with vomiting and septic abortion

While biochemical and renal changes associated with all these conditions are not identical they are sufficiently similar to justify a search for a common etiologic basis Death appears due to renal failure with both biochemical and renal changes differing in many respects from those occurring in any kidney lesion of known etiology There seem to be two possible explanations (1) a metabolic product carried to the kidney by the blood (2) anoxia of the kidney possibly resulting either from a period of hypotension or from a neurogenic vascular disturbance The nephrotoxic theory is doubtful since the toxic substance has not been satisfactorily identified Most evidence to support the second theory is experimental Renal anoxia produced by clamping renal arteries in dogs and rats has resulted in death If the clamp is released after an hour a renal histologic picture not unlike that seen in these cases results Oliguria has been produced by stimulation of splanchnic and peripheral nerves Direct pressure on a limb by continued application of a tourniquet has produced extensive retrograde arterial spasm Obviously persistent hypotension local or general might produce renal anoxia Such an explanation has been advanced in blackwater fever A diminished blood supply might account for the histologic appearance in these cases particularly changes in the arterioles and the fact that those functioning portions of the kidney best supplied with blood have suffered

Sedimentation of these suspended crystals occurs in the terminal portions of the collecting tubules and in the renal calix Proximity of crystals here results in aggregation and formation of concretions that obstruct the terminal portions of the collecting tubules This process progresses in a retrograde manner up the collecting tubules Calyceal concretions remain in situ or pass down the ureter much as do ordinary urinary calculi

Traumatic Uremia E M Darmady, A H M Siddons T C Corson C D Langton Z Vitek A W Badenoch and J C Scott[1] report eight cases (six fatal) in young soldiers a few days after they were wounded by high explosive missiles Injuries were severe but did not seem sufficient to cause death Oliguria vomiting and increased blood urea developed in all The case were seen among 2,000 selected casualties from northern France in a transit air evacuation hospital and the 6 fatal cases accounted for a third of the deaths in the hospital

Autopsies in four cases showed the kidneys larger than normal On section the capsule was under tension and the cut surface swollen and everted Demarcation of the kidneys was enhanced by the pale glistening and rather granular cortexes The pelves showed slight congestion of surface vessels but no evidence of crystalline or amorphous deposits There was no evidence of antemortem thrombosis in the major blood vessels

In searching for a possible causative factor certain features seemed noteworthy (1) Injuries in all cases were caused by high explosives (2) There was considerable injury to the extremities in all, in none was there crushing injury nor was the local condition sufficient to account for death (3) Low blood pressure was recorded at some stage in five cases (4) There was a lesion of a major vessel in six cases (5) All patients had transfusions with group O blood No clinical evidence of mismatched transfusion was apparent at the time of transfusion Histologically, the appearance of the kidneys in these cases and in cases of mismatched transfusions are

(1) Lancet 2 809 81 Dec 23 1944

cumstances a congo red test will usually establish the diagnosis (Table 1) This test is invariably positive with

TABLE 1—PERCENTAGE OF CONGO RED ABSORBED

DEGREE OF AMYLOIDOSIS	59 OR LESS	60 89	90 99	100	TOTAL
Uremic	1			9	36
Pre uremic	1	0	5	44	50
Moderate		1	2	36	4
Minimal	4	8	3	9	44

hepatosplenomegaly because amyloidosis has developed at least moderately before the organs are enlarged

Sometimes with minimal and usually with moderate renal amyloidosis signs and symptoms of renal involvement first lead to diagnosis If in the course of tuberculosis both albumin and casts appear in the urine in considerable amounts diagnosis of renal amyloidosis may be presumed and later confirmed Urinary concentration is almost always diminished when the urine contains albumin and casts In the early stages of renal amyloidosis a trace of albumin is present Content of albumin usually remains low for months and then gradually increases (Table 2) In some cases it remains low

TABLE —AMOUNT OF ALBUMINURIA

DEGREE OF AMYLOIDOSIS	NONE	TRACE	SMALL	LARGE	TOTAL
Uremic	1 (7)	1 (9%)	5 (10 9%)	39 (84 7%)	46
Pre uremic	0	1 (1 8%)	7 (11 9%)	51 (86 3%)	59
Moderate	10 (15 8%)	13 (17 1%)	23 (0 3%)	8 (6 8%)	76
Minimal	23 (1)	47 (44 %)	[illegible] (20 8%)	14 (13 %)	106

until death in a few albumin may increase rapidly indicating rapidly progressive renal amyloidosis Presence of extensive albuminuria for any considerable time indicates extensive amyloid degeneration of glomeruli and severe renal damage Loss of albumin in the urine

least The anoxia might be due to hypotension or vascular spasm or both This theory merits further attention both clinically and experimentally

Renal Amyloidosis was studied in 468 cases of varying degrees by Oscar Auerbach and Marguerite G Stemmerman (Sea View Hosp, Staten Island N Y) In 12 instances complete gross and microscopic studies of the kidneys were not made In 379 of the remaining 456 cases kidney examination revealed deposition of amyloid Tuberculosis was the causative factor in all but five cases (four of chronic bronchiectasis and one of syphilis) Pulmonary involvement with or without extrapulmonary tuberculosis was the underlying disease in 326 cases In 81 cases there was tuberculosis of bone alone or associated with some other tuberculous process Empyema was present in 115 cases, in all but 7 it was associated with tuberculosis elsewhere In most cases autopsy showed the tuberculous process to be progressive

Study of these 379 cases allowed the authors to follow the course of renal amyloidosis from onset to termination The disease usually develops as part of a generalized process including involvement of spleen, liver and adrenal glands In most cases extent of amyloid involvement of the kidneys lags behind that of the liver and spleen Most patients die of the underlying disease, usually tuberculosis or its complications Hence many patients with amyloidosis die with minimal or moderate renal involvement In a relatively small proportion the amyloid process continues for a long period In some instances amyloid degeneration progresses after the underlying disease has healed It is in these that renal insufficiency usually develops and patients often succumb to uremia During progressive deposition of amyloid, the typical clinical picture of nephrosis often develops

In early stages of amyloidosis there are often no diagnostic signs or symptoms Hepatomegaly or splenomegaly may suggest generalized amyloidosis Under such cir

( ) Arch Int Med 74 44 53 Oct 1944

hyperparathyroidism disturbances in calcium metabolism stasis and infection and disturbance in amino acid metabolism have been studied as etiologic factors Age diet climate and heredity are also considered

Generally renal calculi may be classified as primary or secondary Primary calculi such as calcium oxalate and phosphate ammonium urate uric acid cystine and xanthine are usually deposited in urines of a variable range of acidity Secondary calculi such as calcium carbonate calcium phosphate and ammonium magnesium phosphate are found in alkaline urines Some unusual calculi are composed of albumin and fibrin Recently many cases of sulfonamide concretions have been reported

Symptomatology varies from a practically symptomless state to violent acute manifestations Symptoms depend on size number and situation of calculi and presence of infection and obstruction Calculi may remain quiescent for long periods (especially calyceal stones) then suddenly be extruded into the pelvis and cause acute obstruction Most frequent symptoms are pain pyuria and hematuria Renal calculi often produce symptoms referable to the gastro intestinal tract So-called silent stones are not infrequent and generally are large Asymptomatic calculi may be discovered during routine investigation Presence of red blood cells and pyuria warrant complete urologic study Many patients have been subjected to unnecessary appendix and gallbladder operations or even exploratory operation for a supposed intestinal obstruction due to a reflex ileus

Of 422 cases of renal lithiasis observed over six years bilateral involvement was present in 110 (26 per cent) Many cases thought at first to be unilateral subsequently showed involvement of the other kidney Of 130 patients operated on for unilateral lithiasis and followed for one to seven years 19 (14 6 per cent) later presented evidences of calculous disease in the opposite kidney Bilateral renal lithiasis is serious often progressive and uncontrolled by any type of treatment Surgery is often

causes a decrease in total amount of blood protein, almost invariably present in advanced renal amyloidosis With this there is a tendency toward inversion of the albumin globulin ratio Accompanying albuminuria and generally increasing proportionally is excretion of hyaline and granular casts

It is usually during advanced stages that the clinical picture of nephrosis appears Besides low blood protein, albuminuria and urinary casts the patient has edema of the lower extremities and face and usually fluid in the serous cavities In most patients edema is terminal occurring in the last month of life However, the nephrotic syndrome may continue for several years without clinical evidence of renal insufficiency Although patients with progressive renal amyloidosis may live for years death ensues rather rapidly when renal insufficiency develops

Patients who died of amyloid uremia (in 63 3 per cent developing during the last month) exhibited coma, uriniferous odor of the breath edema and subfebrile temperature Almost all of these patients had previously manifested a typical nephrotic syndrome Twenty four patients who died of uremia had enlarged kidneys with a smooth surface—true amyloid kidneys The authors found no instance of contraction of the kidney due to amyloidosis Whether or not the patient succumbs to amyloid uremia depends on patency of the glomerular capsular space When this is obliterated death from uremia is inevitable

Renal Lithiasis and Its Treatment A Hyman[3] (Mt Sinai Hosp New York City) states that in many patients especially those with bilateral involvement and multiple recurrences the disease is malignant often uninfluenced by any type of medical or surgical treatment The sequence of calculous obstruction and infection too often ends in irreparable damage and destruction of renal tissue Etiology is obscure Recently vitamin A deficiency a microscopic lesion of the renal papilla

(3) S Clin North Ameri 25 307 324 Ap 1 1945

gery for a silent calculus for if left undisturbed most calculi sooner or later cause obstruction or infection In the case of stag horn calculus unless the condition has progressed so far as to cause marked kidney destruction and chronic pyelonephritic changes operation often offers a better chance of preserving the kidney than a policy of watchful waiting In recurrent renal lithiasis these indications do not always hold true and there should be conservatism toward subjecting the patient to a secondary procedure

Surgical management of unilateral renal calculi should be conservative and nephrectomy should be performed only as a last resort Kidneys almost devoid of function may recover remarkably after removal of the calculus and establishment of free drainage In operating for bilateral renal calculus the better of the two kidneys should be operated on first though certain factors may reverse the decision The kidney responsible for pain hematuria and pyelonephritis should be given prior consideration Whenever possible the calculus causing obstruction should be removed first Bilateral simultaneous operations for dendritic calculi should never be performed Difficult problems may be presented in bilateral lithiases especially when complicated with a ureteral calculus

Incidence of recurrence of renal lithiasis after conservative surgery will depend on the chemistry of stone infection type of operation performed and duration of follow up observations Surgery is just one phase in treatment An attempt should be made to eradicate infection and eliminate stasis focal infections should be cleared up and a proper dietary regimen instituted Sulfonamides mandelic acid and penicillin are available to combat infection For uric acid cystine and xanthine calculi an alkaline ash diet is prescribed For oxalate calculi all foods with high oxalate content should be prohibited Phosphate and carbonate calculi require an acid ash diet and maintenance of urinary pH around 5 2 Vitamin A should be given in large doses 50 000

useless except to relieve an acute condition for some patients are stone formers whose metabolism cannot be influenced Recurrence follows on recurrence, first one kidney is involved, then the other These cases are practically always complicated by obstruction stasis and infection with gram negative organisms, especially enterococcus and proteus types The patients are resistant to dietary regulations and chemotherapy Ultimately there is so much kidney destruction that death ensues from renal insufficiency Occasionally there will be variations in composition of the stone

Complete urologic investigation entails careful urinalysis roentgenography, pyelography and cystoscopy Approximately 10–15 per cent of renal calculi fail to visualize in plain films Uratic and uric acid stones either do not cast a shadow or if they do, visualize faintly Intravenous urography is essential, or if means are not available cystoscopy and ureteral catheterization combined with pyelography The type of stone can frequently be diagnosed by finding crystals in the urine, this is especially important in cystine stones Bilateral ureteral catheterization combined with functional tests separate urines for culture and pH determination complete the investigation

Dietary treatment of urinary lithiasis has been disappointing, except for cystine calculi which have been dissolved by a high alkaline ash diet reinforced by sodium bicarbonate Since this type can be diagnosed by finding crystals in the urine a high acid ash and vitamin diet should be tried 10–12 months provided the stone does not cause obstruction and infection

Use of solution G (sodium citrate citric acid solution with magnesium) is difficult and requires meticulous care, but in selected cases, especially recurrences it should be tried

Surgery is indicated if the calculus produces pain or colic and is of such size that spontaneous passage is questionable Any calculus that causes infection and obstruction should be removed The consensus favors sur

lesions often heal spontaneously Medlar believes that tuberculous bacilluria means renal tuberculosis

Following development of early cortical lesions one of three courses may ensue (1) the lesion may heal as any other tubercle (2) the lesion may be merely part of an overwhelming miliary tuberculosis and the patient may die usually without primary symptoms, or (3) chronic renal infection may be established which usually progresses and may be bilateral from onset The clinical picture of renal tuberculosis is not prominent until the bladder is invaded To make diagnoses earlier routine urinalysis should be done on patients with totally unrelated complaints and symptomless pyuria should always be investigated In patients with known tuberculous infection elsewhere periodic urinalysis should be routine Diagnosis is established by finding tubercle bacilli in the urine If the disease is suspected every effort should be made to identify the organism by staining the sediment in a 24 hour specimen guinea pig inoculation and urine culture These tests must be done repeatedly in some cases before one can be sure the organism is not present If the organism cannot be found but renal tuberculosis is still suspected retrograde pyelograms should be made and specimens from each ureter similarly examined

Once diagnosis is established it is necessary to decide whether surgery is indicated If the disease is unilateral and advanced and the contralateral kidney is normal by pyelography removal of the diseased kidney is indicated However tuberculosis elsewhere may be a factor in this decision In very early renal tuberculosis, with pus and bacilluria but no pyelographic changes the trend is toward conservative medical treatment When renal infection is bilateral surgery is not indicated unless far advanced destruction is present in one kidney and only minimal disease in the other

units daily and a large fluid intake is important Patients confined to bed with fractures or bone disease should be placed on a high vitamin A and acid ash diet fluids should be forced and active and passive motion of limbs not involved should be practiced Roentgenograms should be made every three to six months for several years and intravenous urograms should be taken occasionally

Renal Tuberculosis is discussed by William G Gordon[4] (Univ of Kansas) Although it is relatively uncommon renal tuberculosis is encountered often enough to be considered in differential diagnosis of any refractory urinary infection Early diagnosis is imperative for optimal therapeutic results The kidney infection should be diagnosed and treatment instituted before bladder infection occurs

Tuberculosis is never primary in the kidney but is carried there by the blood from a primary focus elsewhere or from an established secondary focus Sometimes an active infection elsewhere can be demonstrated, but often this is not possible Medlar produced renal tuberculosis in guinea pigs and rabbits and found that initial renal tubercles were multiple and that bilateral focal infections were the rule (88 per cent) Initial tubercles occurred usually in the cortical zone, where blood flow is slowed in the glomerulus and occasionally in the corticopyramidal or medullary areas Subsequently Medlar examined by serial section 44 kidneys of 30 patients dying of tuberculosis without urinary symptoms In 2 cases no renal tuberculosis was found in 22 there were definite renal lesions containing tubercle bacilli with scars of healed lesions in 14 cases in the remaining 6 only healed scars were found Distribution of active lesions was predominantly cortical (75 per cent) although some were corticomedullary and some medullary If Medlar's interpretation of the scarring is correct, it suggests that the disease is hematogenous and bilateral at least at onset More important it proves that initial

(4) J Kansas M S c 45 341 343 October 1944

DISEASES *of the* HEART *and* BLOOD VESSELS

WILLIAM D STROUD M.D.

PART IV

DISEASES OF THE HEART AND BLOOD VESSELS

INTRODUCTION

In this series as during the past 15 years the articles will be found grouped under the headings as outlined in the nomenclature and criteria for d agnosis of diseases of the l e t r used by the Criteria Committee of the New York Heart Association (Arthur C DeGraff M D Clarence E de la Chapelle M D Cary Eggleston M D Charles E Kossmann M D Robert L Le y M D John B Schwedel, M D and Harold E B Iardee M D chairman) Th s nomenclature and criteria for di gnos s ha e been ap p o ed by the American Heart Association and copies may be obtained through its ma n office at 1 90 Broadway New York City

The Ed tor wi hes to express his s n ere appreciation for the valu able assistance of Dr C Alexander Hatfield in re iewi g the lit erature of the past year dealing with per pheral vascular d sease

—WILLIAM D STROUD

ETIOLOGIC DIAGNOSIS

ARTERIOSCLEROSIS

Normal Heart in Old Age A basic difficulty in most studies of the heart in old age is the decision concerning which changes constitute disease and which are those of normal senescence A Stone Freedberg and Herbert D Lewis[1] (Harvard Univ) state that gross changes with age include tendency to pericardial opacity decreased size of the left ventricular apex increase of subpericar dial fat along grooves for the coronary vessels valvular rigidity deepening of the sinuses of Valsalva and valvu lar sclerosis Microscopic changes of involution include loss of power of cell division with fewer mitoses quanti tative atrophy with fewer and smaller cells condensa tion of chromatin of the nucleus nuclear pyknosis vacuolation and karyolysis and lipoid deposition in the

(1) N w E gl d J M d 31 731 738 N 30 1944

Pathogenesis of Atherosclerosis L N Katz and D V Dauber[2] (Michael Reese Hosp) believe that cholesterol plays a key role in atherosclerosis and is essential in development of atheroma Furthermore thyroid hormone and thyroid stimulating hormone affect the rate of transport and storage of cholesterol thereby playing an essential part in the genesis of atherosclerosis Localization of lesions is influenced by physiologic maturation and differentiation of the intima which goes on to age 30 particularly in the epicardial portion of the coronary arteries and in the aorta generally but more marked at certain sites Development of vasa vasorum in the intima with openings in the arterial lumen likewise determines the localization of lesions When hypertension occurs on whatever basis it hastens development of atheroma But hypertension alone without action of the cholesterol factor will not produce atheroma Syphilis rheumatic arteritis and other inflammatory arterial diseases may augment atherosclerosis by increasing both local tissue factors i e intimal thickening and number of vasa vasorum

Moenckeberg s Sclerosis Clinical Entity Samuel Silbert and Heinz I Lippmann[3] (New York City) state that clinical characteristics which distinguish Moenckeberg s sclerosis from other forms of arteriosclerosis are extreme calcification of leg arteries in young or middle aged persons without signs of impaired circulation Calcification of the blood vessels is usually discovered accidentally in roentgenograms Physician and patient are frequently so surprised by the unusual findings that treatment of the condition for which roentgen examination was made is neglected and measures are immediately instituted to improve circulation the fact that the circulation is entirely normal is completely disregarded Actually the prognosis of Moenckeberg s sclerosis is favorable Patients observed for years have shown no tendency to develop impaired circulation or other serious sequelae

(2) J Mt S H p 1 38 410 M J n 194
(3) Ibid pp 689 700

cytoplasm Vascular changes such as atherosclerosis, loss of elastic tissue and muscle cells and calcium deposition are frequent

Whether arteriosclerosis is to be regarded as a senescent change or attributed to some disease of unknown origin is unsettled Whether or not coronary arteriosclerosis is a disease occlusions are found in 40 per cent of males over 55 Development of anastomoses does not occur with progressive age, which may partly explain increased mortality in initial attacks of myocardial infarction in old persons No correlation between changes in radial arteries and coronary arterial disease exists

Pulse rate is said to increase slightly after 65 The carotid sinus reflex becomes more sensitive with age Cardiac output is normal at rest but this is no index of the heart s ability to act under stress Vital capacity is only slightly decreased at 40–50 but shows a rapid and progressive decline in older persons There are no significant changes in acid base balance Venous pressure is normal Pulse wave velocity of the radial artery and aorta shows increase with age

Diagnosis of congestive heart failure in the aged based on dyspnea, slight cyanosis basal rales and palpable liver edge is too common Pulmonary diseases such as emphysema pulmonary fibrosis mild chronic bronchitis and atelectasis are much oftener responsible for these symptoms and physical findings Peripheral edema particularly that occurring as an isolated finding is more usually due to nutritional deficiencies varicose veins intra abdominal tumors and obesity than to congestive heart failure Chest pain related to cervical or thoracic osteo arthritis hiatus hernia or gallbladder disease is too frequently labeled angina pectoris A careful history is usually all that is needed to differentiate these conditions

[Of course old age is a relative term But it is my impression that physicians advise more restrictions and thus cause unhappiness in older people than are necessary I doubt that the e restriction prolong life and I believe that they u uall mak the remain ng years less happy —Ed]

tablished Future work on sulfonamides penicillin and similar preparations may ultimately provide satisfactory treatment Also continued emphasis on relationship be tween valvular disease congenital heart disease and sub acute bacterial endocarditis will lead to earlier diagnosis and more successful therapy

Subacute Bacterial Endocarditis Pathology F A Willius states that a previously damaged valve or a con genital cardiac defect is a prerequisite for development of subacute bacterial endocarditis Valves injured by previ ous rheumatic fever are seen most frequently and the mitral and aortic valves are the seat of the disease more often than are valves of the right side of the heart The valvular deformity mechanically may have been rela tively insignificant and if subacute bacterial endocar ditis had not occurred many of the patients would have had years of comparatively good health and frequently a normal life expectancy

Numerous congenital defects permit development of subacute bacterial endocarditis or endarteritis Aortic valves damaged by syphilis and syphilitic aortitis with out involvement of aortic valves occasionally and arterio-sclerotic valves only seldom are the seats of subacute bacterial endocarditis

The vegetations are composed of irregular masses of fibrin cellular elements of blood and platelets enclosing micro organisms The last frequently adhere to the sur face of the vegetation The vegetations are usually de cidedly larger than those found in rheumatic endocar ditis but not often as large as those in acute bacterial endocarditis They may involve the chordae tendineae and the mural endocardium of the left auricle and ven tricle from direct extension or contact At times the intima of the aorta becomes involved Occasionally an ulcerative process occurs particularly of the aortic valves which may eventuate in perforation of the cusps

Early in the disease embolic detachment of bacteria

(5) P St E M t M y Cl n 19 497 503 Oct 4 1944

Moenckeberg's sclerosis is characterized by a deposit of calcium in the media of the arteries There is no thickening of the intimal layer (the most striking feature in true arteriosclerosis) and the blood vessel lumen is therefore not narrowed Surface of the intima remains uninjured and thrombosis does not occur Roentgenologically typical cases show calcification of leg arteries in the form of a chain of rings like a goose neck Calcification may extend upward beyond the pelvic brim and may be found in the brachial artery Clinical features are complete absence of evidence of impaired circulation in the extremities All pulsations are easily felt and are normal Oscillometric and temperature studies indicate normal blood flow No thickening of blood vessels is noted on palpation The authors 14 patients have been males

Bacterial Infection

Endocarditis Ralph H Major[4] (Univ of Kansas) discusses the history symptoms and treatment Subacute bacterial endocarditis as a clinical entity is caused by Streptococcus viridans and other types of endocarditis should perhaps be called pneumococcic or gonococcic etc In most cases onset of symptoms is insidious and in early stages symptoms may seem so slight that it is difficult to convince the family that the disease is serious and usually fatal As the disease progresses the patient slowly loses weight, appetite fails and anemia which may not have been marked in the beginning becomes more pronounced fever tends to rise higher and petechiae become more numerous Duration varies within wide limits according to virulence of the organism individual resistance condition of the heart at onset and frequency and location of emboli Average duration is about six months

The percentage of recovery remains low and the complete therapeutic answer has not been found with sulfonamides The best results from sulfonamides may be expected when they are used as soon as diagnosis is es

(4) J Oklahoma M A 37 5 7 532 December 1944

into a Petri dish at the bedside Such cultures are valuable for prognosis in both staphylococcic and streptococcic septicemia and records of cure without this check should be accepted cautiously

In three patients repeated isolation of group B streptococcus from the blood clinical evidence of generalized infection and with one exception absence of an extracardiac focus were strong presumptive evidence of endocarditis even before signs of valvular damage appeared Although endocarditis was diagnosed in only one of the three patients before penicillin treatment unequivocal signs of endocardial involvement with embolic phenomena developed in all in one diagnosis was confirmed at autopsy In only one was there definite evidence of antecedent valvular damage (following acute rheumatic fever) indicating that group B streptococci may attack healthy heart valves Obstruction in large leg vessels in all three patients (followed by foot gangrene in one) was probably due to arterial embolism from friable endocardial vegetations There was no evidence of cardiac failure or auricular fibrillation conditions which also predispose to arterial block

Of two patients with staphylococcic septicemia signs of endocarditis were present in one on admission Although diagnosis was confirmed at autopsy the small size of the vegetations and the repeatedly negative blood cultures during penicillin therapy were evidence that staphylococcic infection had been controlled Treatment however was begun too late irremediable damage had been done and the patient died of uremia The other patient had two septicemic relapses and evidence of endocardial damage in the form of an aortic diastolic murmur was noted for the first time during the second relapse although hematuria anemia and persistent tachycardia were present earlier The aortic diastolic murmur hematuria and negative evidence of antecedent syphilitic or rheumatic infection were accepted as proof of development of bacterial endocarditis Although the

bearing vegetations occurs The site of the vegetations determines the route of dissemination of emboli Vegetations on the mitral and aortic valves or implanted on the intima of the aorta allow embolic detachments to enter the systemic arterial blood stream directly Vegetations on the tricuspid and pulmonary valves (rare in subacute bacterial endocarditis) unless complicated by a congenital communication between right and left side of the heart or a septal perforation by a mycotic process limit dissemination of emboli to the pulmonary circulation and their lodgment in the lungs sometimes leading to diagnosis of pneumonia With such congenital abnormalities as defects of the interauricular and interventricular septum or patency of the ductus arteriosus vegetations may extend to both the right and the left surface of the abnormal communication permitting dissemination of emboli into both pulmonary and systemic arterial circulations

Common sites of lodgment of emboli are arterioles of the skin mucous membranes and retinas and the spleen kidneys arteries and other vascular structures and the central nervous system Varying inflammatory tissue change occur depending on the characteristic response of the organ or tissue concerned

Penicillin Therapy in Acute Bacterial Endocarditis A Dolphin and R Cruickshank[8] (Hampstead) report on six unselected patients with acute bacterial endocarditis treated consecutively in a puerperal sepsis unit Three infections were due to hemolytic streptococci group B one to hemolytic streptococcus group A and two to Staphylococcus aureus

Infecting organisms in all cases were sensitive to penicillin by in vitro tests Blood and urinary levels of penicillin were determined Penicillinase was added to blood cultures in fluid mediums Quantitative blood cultures were made repeatedly in all cases by adding 1 cc blood to a tube containing 1–12 cc melted agar and pouring

(8) Brit M J 1 897 901 June 30 1945

tial usefulness of the drug However as this is not always true the therapeutic effect should probably be tried When the patient is desperately ill penicillin should be started immediately and bacterial testing done simultaneously

It is thought best to give large doses of penicillin preferably 10 000–20 000 units every two hours by combined repeated intravenous and intramuscular injections Often repeated injections are given intravenously during the day and intramuscular injections (usually in the buttock) at night However injections must be maintained at regular intervals so that the blood level of penicillin is always high In addition to penicillin use of any other substances which may retard bacterial growth or build up the patient s resistance is justified Repeated use daily or every few days of perfectly matched whole blood in small quantities to keep blood count at or near normal level should be continued throughout treatment Blood cultures should be repeated regularly always with addition of clarase because without it one may have what appears to be a negative culture when in reality all one has is the local bactericidal effect of penicillin in the culture medium Treatment with penicillin should be continued until the blood culture is persistently negative until all signs of activity such as fever tachycardia and rapidly changing heart sounds disappear and preferably until the sedimentation rate returns to normal

Response to treatment may be dramatic or slow with the infection controlled only after months Sometimes temporary response is followed by seeming resistance to the drug and death due to embolic phenomena or to cardiac failure Generally the longer the duration of the disease the longer the time before arrest is established Poindexter treated one patient over nine months before blood cultures remained persistently negative Treatment is difficult unless arrest occurs promptly Months of injections at two hour intervals is a stupendous task for both physician and patient and treatment is expensive

valvular lesion was still present, the patient was well 10 months after discharge

Signs of fresh endocardial damage developed in the patient with group A streptococcic septicemia during her illness She had a history of mitral stenosis and had an apical systolic but no diastolic or aortic murmur Blood cultures were persistently positive despite intensive sulfonamide therapy and tachycardia anemia and progressive wasting were present About the time penicillin therapy was begun Osler s nodes and hematuria appeared and four days later an aortic diastolic murmur When discharged and at examination one month later she had aortic regurgitation in addition to mitral stenosis

The favorable response to moderate dosage of penicillin is interesting in view of failure of similar dosage in subacute bacterial endocarditis Perhaps the infecting organism is more sensitive to penicillin or perhaps the more bulky and friable vegetations allow penicillin to permeate the clot more easily Although three patients were well 6–12 months after penicillin therapy was stopped it is impossible to say what the long term prognosis will be With gross valvular damage a heavy strain is put on cardiac reserve and patients are at the mercy of any infection that may lead to bacteremia and a fresh endocardial infection

Use of Penicillin in Treatment of Subacute Bacterial Endocarditis Due to Streptococcus Viridans is discussed by Charles A Poindexter (New York City) Among conflicting opinions on routine treatment of this disease one concerns combined use of heparin and penicillin Only continued study will show whether heparin is beneficial Apparently best results are obtained by the following procedures Blood cultures are taken on three successive days Bacteria isolated from culture are tested for strain and for penicillin susceptibility in varying dilutions Susceptibility in vitro usually indicates poten

(7) Mod Concepts Cardiovascular Dis v 13 No 11 November 1944

days and reached a saturation of 83 8 per cent 14 days after operation Red blood cell count fell from 10 000 000 to 6 000 000 hemoglobin from 26 to 20 Gm and hematocrit reading from 81 to 53

It appears that this type of patient can tolerate inhalation anesthesia The first patient was only 14 months old and weighed less than 9 lb Ether by open drip was used during most of the procedure as a closed system small enough was not available In the other patients cyclopropane with a high concentration of oxygen was used Oxygen content of arterial blood was apparently increased and cyanosis was definitely lessened. Cyanosis did not appear to be greatly increased during the period of occlusion of a main pulmonary artery while anastomosis was being performed There was little evidence of impairment of circulation to the brain or arm deprived of their major arterial pathway Pulse was absent for some time postoperatively and the part was slightly cooler than the opposite side but immediately after operation it was evident that circulation was adequate to maintain life of the part

Types of abnormalities which should be benefited by this operation are the tetralogy of Fallot pulmonary atresia with or without dextroposition of the aorta and with or without defective development of the right ventricle truncus arteriosus with bronchial arteries and a single ventricle with a rudimentary outlet chamber in which the pulmonary artery is diminutive Operation is indicated only when there is clinical and cardiologic evidence of a decrease in pulmonary blood flow The operation is not indicated in cases of complete transposition of the great vessels or in the so called tetralogy of Fallot of the Eisenmenger type and probably not in aortic atresia The operation should not be performed when studies reveal a prominent pulmonary conus or pulsations at the hili of the lungs

Surgical Treatment of Patent Ductus Arteriosus is discussed by Arlie R Barnes and Stuart W Harrington[9] (Rochester Minn) Two minimal requirements for

(9) Mod. Concepts Card v 1 D 1 14 F b ry 1945

It seems hardly possible that any treatment will offer a high percentage of cures, but penicillin may arrest the process and is a marked advance over any drug hitherto used

[Intramuscular injections are much less painful if they are given with novocain —Ed]

Congenital Anomaly

Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia Alfred Blalock and Helen B Taussig[8] (Johns Hopkins Univ) describe operations in three cases differing in detail but greatly increasing the volume of blood reaching the lungs

Case 1 —The end of the left subclavian artery was anastomosed to the side of the left pulmonary artery As the baby was small and weak extensive laboratory studies were not performed She was no longer able to sit alone had refused feedings and had lost weight Red blood cell count had fallen from 7 000 000 to 5 000 000, and cyanosis had diminished considerably After operation, clinical improvement was remarkable Appetite has improved she has gained weight and is only occasionally cyanotic

Case 2 —Presence of a right aortic arch made anastomosis of the innominate artery to the left pulmonary artery possible The patient, 12 was deeply cyanotic and could not walk 30 ft without panting Two and a half weeks after operation she walked 60 ft rested a short time and walked 60 ft back to her room and sat down quietly Oxygen saturation of the blood which was 36.3 per cent before operation rose to 82 8 per cent three weeks later Red blood cell count dropped from 7,500,000 to 6 000 000, hemoglobin from 24 to 17 5 Gm and hematocrit reading from 71 to 55

Case 3—Since the aorta was in the normal position, in order to use the innominate artery operation was performed on the right side The end of the innominate artery was anastomosed to the side of the right pulmonary artery The boy, 6 improved dramatically Cyanosis was intense before operation, lips were dark purple and he was unable to take even a few steps The day after operation he lay in an oxygen tent with cherry red lips, and color remained good when he was removed from the tent He changed from a miserable whining child to a happy smiling boy Permission to walk was delayed because of persistent low grade fever, but after three weeks he could walk 40 ft without panting or becoming cyanotic Oxygen saturation of arterial blood rose from 35 5 to 79 7 per cent in 9

(8) J A M A. 128 189 07 May 19 1945

difficult to decide that surgical closure in cases of compensated patent ductus is not indicated especially when skilled surgeons can anticipate a mortality of about 5 *per cent in cases in which there is no infection*

Harrington has operated on 10 patients indications were minor episodes suggesting impending cardiac insufficiency in 4 congestive heart failure prior to admission in 3 and subacute bacterial endocarditis in 3 Death occurred from uncontrollable hemorrhage at operation in one case of subacute bacterial endocarditis One patient who had subacute bacterial endocarditis was well 20 months after operation and one remained well for 6½ months after operation then died of rupture of an aneurysm *Operation should be performed promptly* without awaiting attempts to sterilize the blood stream once subacute bacterial endocarditis in association with patent ductus arteriosus is diagnosed Blood cultures obtained immediately after closure of the patent ductus in two of the authors cases of subacute bacterial endocarditis were negative and remained so whereas before operation cultures were positive

Patent Ductus Arteriosus and Its Surgical Treatment A Rae Gilchrist[1] (Royal Infirm Edinburgh) reports a study of *patent ductus arteriosus* in 28 consecutive patients 14 of whom underwent surgical ligation In diagnosis the continuous murmur of Gibson is almost pathognomonic In its absence diagnosis can be established by detection of other signs which together are of almost equal value In order of importance these are pulmonary artery dilatation increased pulse pressure at rest or *after exercise and a long harsh basal systolic murmur* with an accentuated or reduplicated pulmonary second sound

Repeated roentgen examinations are valuable Radiologic appearances are on occasions unique the changing pattern of the heart and lungs makes a sequence so characteristic that diagnosis of bacterial endarteritis of

(1) B H J 1 J 136 Ja ry 1945

diagnosis of patent ductus arteriosus are a continuous murmur over the pulmonic region and roentgen evidence of enlargement of the pulmonary conus The latter sign may be lacking occasionally The machinery like murmur must be heard in diastole as well as systole A stethocardiogram taken over the pulmonary artery is useful in establishing the continuous character of the murmur It may be accentuated just before, during or after the second sound A thrill may be felt at the point of greatest intensity of the murmur in about 75-80 per cent The thrill cannot be excluded unless palpation is carried out on deep inspiration with the patient leaning forward Roentgen signs of uncompensated patency of the ductus arteriosus include enlargement of the left ventricle increased pulsation of left ventricle and pulmonary artery pulmonary congestion and evidence of dilatation of the left auricle The blood pressure reveals increased pulse pressure the average in one series being 59 mm Hg The electrocardiogram reveals no axis deviation or only slight deviation Patency of the ductus arteriosus in infancy is usually complicated by other congenital cardiac defects However few patients with these complications live over three years so in adults the chances are good that patent ductus is not complicated by other defects

Indications usually given for surgical closure of the patent ductus arteriosus are (1) stunted growth (2) uncompensated patent ductus arteriosus (indicated by lowered diastolic pressure high pulse pressure and collapsing pulse) with an enlarging heart or symptoms of increasing dyspnea or both and (3) presence of subacute bacterial endocarditis Retarded physical development did not constitute an indication for surgery in any of the authors cases but they consider the other two conditions an indication for ligation

Operation may be deferred at least until the child is 6 if he is developing normally and if signs of uncompensated cardiac disease do not appear However in view of mortality statistics for patent ductus arteriosus, it is

the pulmonary artery range of its expansion state of various heart chambers particularly the left ventricle and extent of systolic excursion Systolic excursion taken with the degree of pulsation in the pulmonary artery



F 77—T l tg gr m Enl ged h rt n h ld 4 with greatly e sed cul ty f l ng d p m n t b h f pulm n ry artery pulm ary is t p m t P te t du t rt us c nfirmed at per t

is almost always increased and confirms the nature of the defect Other x ray signs are dilatation of the right and left pulmonary artery branches congestion of lung fields as shown by a diffuse mottling radiating out from the hili toward the periphery hilar dance systolic expansion in the arteries of the lung root and dilatation of the left auricle the last two being least common in

the ductus and pulmonary artery should seldom be missed

Enlargement of the pulmonary artery is usually evident in the frontal view (Fig 76) The artery extends

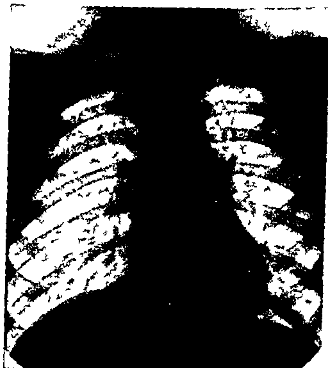


Fig 76 —Tel tg n g m Cha a t tf b t outlin of pat nt d ctus arte os n y th, 18 H t a z w tl n no m l l m ts but p lmonary arc mak s prom n t b lge l l w rt k t n a d vas ula ity f lung fields

to the left as a semicircular shadow between the aortic knuckle above and the ventricular mass below Evidence of pulmonary dilatation was lacking in only 3 of 27 patients examined roentgenographically (Fig 77) In the right oblique position the trunk of the vessel can often be rendered prominent as a bulge over the upper third of the ventricular shadow Fluoroscopy discloses size of

fection in which cure was effected by ligation of the ductus arteriosus (date of operation Dec 5 1939) Of the first five patients four were alive and well three to five years and six of the nine two to five years after operation with no recurrence of symptoms infection or cardiac disability The infecting organism in Case 1 was Haemophilus para influenzae in seven others Streptococcus viridans and in one the infection was apparently mixed Staphylococcus aureus and Streptococcus viridans The late effect of ligation on heart size is *shown in roentgenograms taken about a year and a half* apart in Case 2 (Figs 78 and 79)

The classic thrill and murmur are generally ascribed to rapid flow of blood from the aorta to the pulmonary artery presumably occurring when aortic pressure is higher i e during systole and early diastole Compression of the patent ductus during operation obliterates the thrill in nearly every case thus largely confirming this theory However certain observations suggest that this explanation is not complete In Case 2 application of one ligature reduced but did not abolish the thrill which disappeared only after a second ligature had obliterated more of the lumen In the same case diastolic murmur at first disappeared but returned much less in volume 17 months after ligation although the transverse diameter of the heart had diminished by 2 cm and blood pressure remained normal In another case diastolic murmur disappeared for two weeks and then fully returned yet at autopsy seven weeks after operation the pulmonary end of the ductus was so blocked by a massive clot that water injected into the aorta failed to pass There was however an aneurysm of the ductus patent to the aorta and 3 cm in diameter Hence although the thrill and murmur are largely caused in the usually accepted fashion patency of the ductus may occur without these signs and these signs may be present without patency in exceptional cases

Immediately after ligation a great rise in diastolic

Gilchrist s experience Gross enlargement of the heart is uncommon in uncomplicated cases Striking cardiac en largement suggests complicating factors either some as sociated congenital flaw or an infected ductus and pul monary artery

Most cases are observed in childhood and 70 per cent are detected before age 20 The scanty number of adults can be explained by death in youth spontaneous closure of the ductus in childhood or lack of systematic search for this lesion in older patients

In selection of patients for surgery, main factors are age and degree of cardiac embarrassment In general the younger patient should be accepted for surgery when symptoms are minimal, in the hope that by ductal occlu sion the child may grow and develop normally In older patients surgery can be justified only when symptoms warrant the risk In the presence of an infected ductus ligation should be undertaken without delay at any age

Of 14 patients in whom surgery was judged unneces sary or undesirable the eldest was 49 and the youngest 5, average age 20 Two died one of intercurrent infec tion and one of subacute bacterial endarteritis Slight deterioration in physical capacity was observed in three Two women married and bore children without undue distress In one patient a boy of 6 the ductus closed spontaneou ly Of 14 patients operated on, distinct im provement in general health and physical capacity was observed in 6 Four obtained less benefit than anticipated chiefly because complete obliteration of the ductus was not always obtained Two patients died after operation Two patients operated on for bacterial endarteritis died Death in each instance was attributed to massive pulmo nary collapse

[It is my impression more of these patients are being operated upon than is justifiable —Ed]

Ligation of Patent Ductus Arteriosus in nine cases with infection and in two noninfected cases is reported by Geoffrey Bourne[2] Case 1 was the first case with in

(2) Brit H art J 7 91 94 April 1945

held Seven days after ligation the patient became completely afebrile and blood culture previously positive for Streptococcus viridans became negative and remained so

Results with sulfonamides were disappointing In one

FIG 79—S m se p eced g M h 23 194 ft l g t e f p te t du t s rte su Tr n diam t f heart n w 1 5 cm he rt t rmal nd n l ge nl ged

case sulfapyridine sterilized the blood and eliminated fever for 12 days preceding operation In all other cases sulfonamides failed This suggests that no advantage is obtained by instituting chemotherapy if the patient s condition is reasonably good However it should be used to modify severity of toxemia preoperatively in patients who are critically ill It is also valuable after operation when infection persists



procedure is not without danger Future developments in chemotherapy or treatment by penicillin may strengthen the conservative attitude of watching such patients and reserving surgery until actual onset of infection

EFFORT SYNDROME

Effort Syndrome in the West African Soldier Deryck L H Goddard[3] reports 12 cases in West African Negro soldiers and discusses possible predisposing causes The soldiers recruited in the Gold Coast were supplied by the three main districts Northern Territories 53 per cent Ashanti 10 per cent Gold Coast Colony 34 per cent and miscellaneous 3 per cent There was no case of effort syndrome among soldiers from the Northern Territories All 12 patients showed evidence of their contact with Europeans all spoke English all were Christians whereas only 50 per cent of the whole group were Christians

Pesponse to mental conflict and such emotions as anxiety and fear though depending greatly on innate personality is also affected by upbringing education and experiences A crude solution to mental conflict e g conversion hysteria is found more often in the less intelligent while in the more intelligent occur such reactions as effort syndrome which are subtler and less obviously related to the causative emotion In World War I Rivers stated that conversion hysteria was more common in enlisted personnel and effort syndrome in officers and suggested that one possible cause may be found in educational differences the officer being more widely educated and his mental life more complex and varied It is reasonable to apply this hypothesis to the Gold Coast West African as between Colony man and Northern Territories man considering the generally lower plane of intellect found in the West African Patients in this series have on the whole been much influenced by white civilization Their sphere of thought has been

(3) B t M J 1 908 910 J n 30 1945

Ultimate prognosis is good, considering the seriousness of the condition Experience in the surgeon and skill in the anesthetist are vitally important One patient was desperately ill and by ordinary criteria was an unsuitable subject for surgery however, operation was done and the patient made a good recovery No death occurred on the table one patient died 45 minutes after operation In the other two fatal cases (with severe secondary pulmonary sepsis from infected pulmonary emboli) the patients survived seven weeks and four months In two of the fatal cases there was marked cardiac enlargement In the other fatal case the heart was only slightly enlarged and infection of the aortic valve was present In two of these cases an aneurysm of the pulmonary artery with multiple pulmonary infarcts was present Left sided endocarditis was found at autopsy in two aortic endocarditis in one and mitral and aortic endocarditis in the other Increased virulence of infective endocarditis in children apparently influences the prognosis The two youngest patients, 10 and 15, died

Pulmonary embolism and infarction is of two varieties that occurring from growing vegetations and that resulting from fragmentation of clots or vegetations during healing The former occurs before the latter after, operation Preoperative embolism with pleurisy either with radiologic change or visible or palpable at operation, was present in seven of the nine cases Its presence therefore apparently does not influence the prognosis Postoperative embolism is common and equally free from serious danger

Many uninfected patients have been treated by ligation as reported by several authors Principal indications seem to be (1) anticipation of subsequent infection (2) threat of heart failure or (3) failure of children to grow normally It is highly probable that risk of subsequent infection can be prevented by this operation. Risk of infection is great in these cases and operative risk is less in noninfected cases On the other hand, the

Effort Syndrome is defined by J R Forbes[4] (R.N V R) as a group of symptoms chiefly referred to cardiovascular and respiratory systems produced by minimal exertion in individuals in whom no evidence of organic disease is discoverable

Men in the armed forces with effort syndrome fall roughly into two main categories the constitutional group in whom intolerance of effort has been present since earliest recollection frequently accompanied by excessive emotional lability and men of reasonably normal physique who have not exhibited effort intolerance in early life In the latter the condition develops as a response to difficult emotional circumstances

Symptoms vary extremely The commonest consist of breathlessness exhaustion tremulousness dizziness palpitations and precordial pain Amount of exertion required to cause their appearance is a measure of the severity Physical examination fails to disclose evidence of organic disease but usually demonstrates the presence of central emotional disturbance of the autonomic nervous system manifested by emotional tachycardia coarse tremor of hands and tongue fluttering of closed eyelids pupillary dilatation and sweating characteristically confined to axillas palms and soles Tachycardia is strikingly exaggerated by any exertion or excitement but is absent during sleep (an important diagnostic point)

The history is all important At least half the patients have a family history of nerves and neurotic disorders Frequently a relative or close friend has heart trouble Careful questioning usually discloses neurotic traits in childhood and adolescence The patients tend to be constitutionally timid and shrinking with exaggerated fears and easily upset by emotional stimuli They have always been afraid of the dark afraid of being injured afraid of being bullied They usually have done only light sedentary work because they were afraid they wouldn t

(4) J R N M Serv 30 163 1 0 J l 1944

widened and ability to reason increased by knowledge and experience, accompanied by repression of cruder instincts through stricter mental censorship The Northern

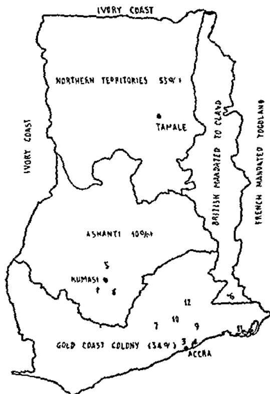


Fig 80 — Incidence of cases (capital towns marked) Figures in parentheses represent percentage of troops serving with R W A F F (Gold Coast) in 1941-4. Case numbers indicate where each patient lived One patient came from Freetown Sierra Leone

Territories man still thinks simply his powers of reasoning are limited and he is much influenced by suggestion During the period under review, many cases of conversion hysteria were observed most of these in Northern Territories men

Prevention of effort syndrome in newly enlisted personnel depends on recognition of the type constitutionally predisposed to it on training such men carefully and gradually and on limiting their work to their physical and psychologic capabilities It is important to watch for the condition during convalescence from illness Any prolongation of palpitations and dizziness in a patient recovering from a disease such as pneumonia should suggest incipient effort syndrome Prompt reassurance and discharge to duty at this stage will cure the condition Further hospitalization will make it worse

Established cases should be quickly assessed It is usually fairly easy to decide from history personality and severity of symptoms which patient is worth treating and which is of no further use in service The former should *not be hospitalized until simple psychotherapy* has been tried in routine surroundings The patient is firmly assured that he is not suffering from organic disease and a simple explanation is given of why he has his symptoms While the man is trying to reorient himself it is well to excuse him from arduous duties but it is a mistake to keep him on light duty more than a week or two He must be encouraged to return to full work at the earliest possible moment and must be persuaded to *stick to it even though he feels tired* Treatment in the hospital is similar and occupational therapy (preferably group work out of doors) is an important adjunct

If effort syndrome is untreated prognosis is poor Even when out of the services only one third of the patients improve on their own whereas by careful rehabilitation two thirds can be sufficiently improved to continue military service

Hypertension

Influence of Age on Blood Pressure Response to Cold Pressor Test Henry I Russek and Burton I Zohman[5] (U S Marine Hosp Staten Island N Y) measured the cold pressor reaction of 350 men over 40 and compared

(6) Am H rt J 9 113 119 J nary 1945

be able to manage' heavier work When such a timid introspective person is thrust suddenly into the armed services his fears multiply a hundred fold The increased burden produces the symptoms of fear, and what was before merely a disability becomes transformed into an illness A physical illness may also provide the trigger initiating an effort syndrome in such a predisposed person This history is so typical that diagnosis is seldom doubtful and special radiologic, laboratory and electrocardiographic studies are unnecessary and undesirable, although in the exceptional case special tests may be necessary The exercise tolerance test ordinarily is a waste of time

Clinical diagnosis can be confirmed by determination of blood lactate values after exercise The normal man drives himself to the point of exhaustion which occurs when blood lactate value reaches 100 mg per cent The patient with effort syndrome does not drive himself to exhaustion he claims to be exhausted before he is

Many physicians diagnose effort syndrome purely negatively only when elaborate investigations have excluded all questions of organic disease Neither a systolic cardiac murmur nor a history of rheumatism nor both, constitutes sufficient evidence on which to diagnose organic heart disease Reliable signs of organic heart disease in men of service age are (1) breathlessness at rest, (2) venous congestion (3) definite clinical and radiologic cardiac enlargement (4) irregular heart rhythm when the heart is beating fast (thus excluding extrasystoles) (5) diastolic cardiac murmur (6) precordial thrill, (7) definite hypertension (systolic pressure at rest over 170 mm or diastolic pressure over 100) Patients with organic heart disease but without obvious failure pericarditis or some such unmistakable condition rarely complain of precordial pain If they do the pain is almost invariably due to a superimposed effort syndrome Precordial pain in a man not obviously ill is not due to heart disease

Prevention of effort syndrome in newly enlisted personnel depends on recognition of the type constitutionally predisposed to it on training such men carefully and gradually and on limiting their work to their physical and psychologic capabilities It is important to watch for the condition during convalescence from illness Any prolongation of palpitations and dizziness in a patient recovering from a disease such as pneumonia should suggest incipient effort syndrome Prompt reassurance and discharge to duty at this stage will cure the condition Further hospitalization will make it worse

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response of persons with initial pressures in the upper *range of normal (prehypertensive) and that of persons* with initial pressures in the lower range of normal (non hypertensive)

It was concluded that response of blood pressure to a standard stimulus of cold tends to increase in all subjects with advancing age Rising response appears to result from increasing irritability of vasomotor centers an effect of vascular changes associated with "aging Tendency for a normal reaction to become 'excessive' is reflected in rising incidence of hyperreaction with succeeding decades There is a marked increase in frequency of hyperreaction with advancing age among 'subjects likely to develop hypertension ' suggesting that such a response is frequently physiologic in later decades of life Hyperreaction is more common among prehypertensives than among nonhypertensives but difference in frequency between respective groups becomes much less pronounced with advance of age The high incidence of hyperreaction among nonhypertensives indicates that such a response cannot be regarded as specific for potential or latent hypertension at this age

[Although the reaction to this test is apparently suggestive in younger people is it wise to let individuals know they are potential hypertensives until there is something we can offer to prevent or treat hypertension?—Ed]

Why Operate for High Blood Pressure? According to Thomas Findley [6] the high mortality from high blood pressure in persons past middle age and failure of medical treatment may justify consideration of surgical intervention in certain cases It is highly unlikely that a single cause of spasmodic contraction of the peripheral vascular bed will ever be found Heredity is significant in degenerative vascular disease but is outside the surgeon s province important endocrine factors are only rarely correctable by surgery and only a few of the renal etiologic factors can be controlled surgically Neurogenic factors, however appear to be of prime importance, and

(6) J Omaha Mid W t Cl n S 6 37 Ap 1 1945

it is in such cases that the surgeon may be helpful

There is no proof that vasospasm characteristic of early hypertension is of nervous origin although in many young persons vasomotor instability seems to be initiated by overactivity of the sympathetic nervous system Sympathectomy may be successful when vasospasm is due wholly or largely to neurogenic influences whereas it obviously would fail in vasospastic states due to inherent arteriolar defects or to circulating pressor substances Therefore careful consideration must be given to the dominating factor before surgery is decided on The consensus is that best surgical results are obtained in young persons with labile blood pressure organically intact blood vessels and overactive nervous system For the young person with fluctuating blood pressure and few symptoms extensive denervation in the splanchnic area and legs should be used When hypertension is relatively fixed blood vessels are diseased and symptoms severe simple adrenal denervation will probably accomplish as much subjective improvement as the more radical procedures Bilateral renal disease is no contraindication and probably many older patients should be considered candidates for this procedure

Sympathectomy is only palliative but until effective medical treatment is provided more operations should be done in hypertensives

Surgical Treatment of Essential Hypertension Mechanism of Action of Sympathectomy C Patiño Mayer Francisco A Pataro Luis Lepera and Vincente F Pataro[7] *observe that the chief obstacle to correct interpretation of the mechanism of sympathectomy is failure to differentiate the organism in repose and in activity* In the kidney for instance two mechanisms regulate renal circulation a permanent humoral and an intermittent neurogenic one which acts only during emotional stimulation Most studies of effects of sympathectomy have been done with the body in repose If such studies

(7) Sema méd 51 467 470 O t 7 1944

were made during activity, the effects would be better understood

Whether or not sympathectomy reduces adrenalin secretion it no doubt prevents oversecretion during emotional stimulation since the connections of the adrenals with the cerebral cortex are severed This inhibition of secretion of adrenalin diminishes vasomotor response which in turn reduces cortical excitability by raising the threshold of excitability Interruption of the nervous connection between cerebral centers and splanchnic area prevents this large vascular field from participating in vasospasm caused by response to emotional stimuli It can also be assumed that splanchnic section suppresses the vascular hypertonia which is maintained by continuous overstimulation of the autonomic nervous system

The effect on the vascular system so important in the splanchnic area is of prime significance in the kidneys Through interruption of nerve pathways emotional factors lose their stimulating and constricting action on the glomerular arterioles this effect being enhanced also by the relative reduction of adrenalin output All this results in diminished secretion of the pressor substance with consequent decrease in cortical excitation and diminished sensitivity of the blood vessels to adrenalin The vicious circle produced by cortical excitation resulting from active and emotional life is thus interrupted or reduced by the operation Sympathectomy may therefore be considered as a brake in critical situations

Transient Hypertension Significance in Terms of Later Development of Sustained Hypertension and Cardiovascular Renal Diseases Robert L Levy (New York City), Charles C Hillman (M C U S A) William D Stroud (Philadelphia) and Paul D White[8] (Boston) analyzed medical records of 22 741 officers of the United States Army to appraise the significance of transient hypertension Blood pressure readings over 150 mm Hg systolic or over 90 diastolic followed by lower readings

(8) J A M A 126 8 9833 N v 25 1944

on other examinations were considered to indicate transient hypertension Length of the observation period was from 1 year to more than 25 years 84 per cent were under observation 5–19 years and 38 per cent 15–19 years In 1 437 instances the observation period was 20 years or more

The frequency with which transient hypertension was first noted increased with age *The curve of increase was* smooth beginning with 5 9 per cent in the age group 25–29 and reaching a plateau of 18 6 per cent at age 50–54 *At all ages sustained hypertension developed* more frequently in those with previous transient hypertension than in those who never showed elevation of blood pressure (Table 1) *In both groups the rate in*creased with advancing years

TABLE 1—LATER OCCURRENCE OF SUSTAINED HYPERTENSION BY AGE IN THOSE WITH AND WITHOUT TRANSIENT HYPERTENSION

Age	Person Years Observed		No. Developing Sustained Hypertension		Rate per Thousand		Ratio
	With Transient Hypertension	Without Transient Hypertension	With Transient Hypertension	Without Transient Hypertension	With Transient Hypertension	Without Transient Hypertension	
[illegible]	1 [illegible]	310 [illegible]	[illegible]	14	[illegible]4	0 5	4 8
0 34	4 401	34 [illegible] 0	11	30	[illegible]	0 9	2 8
35 39	[illegible]	[illegible]18	41	59	[illegible]	1	3.3
40-44	[illegible]	31 501	110	81	11	[illegible]6	4.3
45-49	10 356	[illegible]	[illegible]	[illegible]	[illegible]0	[illegible]	3 8
50 54	8,[illegible]13	1 [illegible]	2 3	133	33 2	[illegible]7	3 4
55-59	[illegible]83	6 508	[illegible]3	97	43 0	14 9	[illegible]

The rate for disability *retirement* with cardiovascular *renal diseases* which *is one index of usefulness of an* officer to the Army was consistently higher among those with transient hypertension than among those without at all ages from 35 to 60 The death rate with cardiovascular renal diseases (Table 2) was also higher in those with transient hypertension and rose in the older age groups Both disability retirement and death rates from diseases other than those of cardiovascular renal origin

were slightly higher in the group with transient hyper tension In the case of retirement rates differences were not significant The higher death rates in the group with

TABLE 2 —DEATH RATE WITH CARDIOVASCULAR RENAL DISEASES BY AGE FOR THOSE WITH AND WITHOUT TRANSIENT HYPERTENSION

Age	Deaths with Cardiovascular Renal Diseases		Rate per Thousand		Ratio
	With Tr Hypertension	Without Tr Hypertension	With Tr Hypertension	Without Tr Hypertension	
25 29	0	7	0 0	0 2	0 0
30 34	1	3	0 2	0 1	2 0
35 39	9	[illegible]	1 2	0 1	12 0
40 44	16	12	1 6	0 4	4 0
45 49	27	0	2 5	1 2	1
50 54	44	30	4 9	[illegible]1	3
55 59	54	6	8 9	5 2	17

transient hypertension were explained partly by the relatively greater number of suicides

The decision as to usefulness to the Army of a man with transient hypertension depends on the need for man power If urgent he may be accepted provided heart arteries and kidneys are normal In doubtful instances examination should include a teleroentgenogram of the heart and an electrocardiogram as well as examination of retinal vessels and urine A few will develop perma nent hypertension and the number will increase as age advances in the authors series the rate per thousand ranged from 5 6 at 35–39 to 48 0 at 55–59 When the need for men in the service is not acute the transient hypertensive is not to be regarded as a first rate risk

Although as a group those showing transient elevation of blood pressure are more likely later to develop sus tained hypertension and various manifestations of car diovascular renal disease this sequence is not invariable The next problem is to define criteria for recognition of persons in whom transient hypertension is an early sign of future trouble

HYPERTHYROIDISM AND HYPOTHYROIDISM

Thyrocardiacs are discussed by Ambrose L Lockwood[9] (Toronto) One of the commonest etiologic factors in so-called heart disease in the Great Lakes area is degenerating adenomatous goiter Evidently some toxic content is thrown into the blood stream from degenerating adenomas which directly affects heart muscle first evidenced by an occasional extrasystole and by its constant and insidious toxic or stimulating effect leads to chronic myocarditis or nerve block characterized by fibrillation It is astounding how soon after removal of the adenoma the burden on the heart seems to be lifted and distress disappears This is usually reported by patients before they leave the hospital after thyroidectomy

Thyrocardiac disease progresses from intermittent tachycardia after exertion excitement or even a heavy meal to the occasional extrasystoles to persistent extrasystoles and finally to true fibrillation The disease develops gradually over many years In a few patients with long standing thyrocardiac disease months may elapse before myocarditis disappears after operation

Size of the gland bears little relation to severity of thyrocardiac disease Treatment is subtotal thyroidectomy as soon as the patient s condition permits Miraculous cures are constantly seen after subtotal thyroidectomy in patients with late thyrocardiac symptoms Practically all such patients can and should be treated surgically The life saving value of thyroidectomy simplicity of present surgical technics and almost complete absence of mortality should be known to all physicians

Extrathyroid Effects of Thiouracil Therapy Ella H Fishberg and Jefferson Vorzimer[1] (Beth Israel Hosp New York City) report results in 96 cases which seem to indicate that thiouracil reduces basal metabolic rate in all patients with hyperthyroidism However it has serious toxic effects and the patient must be kept under

(9) C d M A J 51 53 5 6 Dec mbe 1944
(1) J A M A 128 915 9 1 July 28 1945

continuous medical observation Precautions to be observed are similar to those governing careful administration of sulfonamides however, no injury to erythrocytes has been noted

The main danger with thiouracil is agranulocytosis Since they noted a definite and sudden granulopenia in 20 per cent of their patients the authors believe a white blood count must be done every second or third day, and the drug must be stopped instantly if there is a sudden drop in total leukocyte count or if the granulocytes drop below 45 per cent If there is a sudden rise in temperature, accompanied by arthralgia myalgia, lymphadenopathy or appearance of a rash, the drug must be discontinued The patient should be told to inform any physician called in of medication being taken so that sulfonamides or other compounds containing the benzene ring are not prescribed The patient should be given only two or three days' supply, just enough to last until the next blood count

Since the drop in white cell count can occur with disconcerting suddenness it is doubtful if long continued routine use of thiouracil is desirable until some method of protecting the bone marrow is perfected Use of pyridoxine in prophylactic doses of 150 mg daily by mouth or 200 mg intravenously when a severe drop in leukocyte count has occurred seems to be most promising

Heart in Myxedema L P Howell reports a case in which it was possible to compare cardiovascular findings before appearance of myxedema with findings at the time of its appearance and after 2½ years of its control

Woman 6? was first examined and treated for carcinoma of the breast in June 1939 She returned in February 1940 with symptoms of myxedema and was seen at intervals thereafter until her last admission in August 1942 Roentgenograms left no doubt that cardiac enlargement and subsequent shrinkage coincided with appearance and control of the myxedema Fluctuation in cardiac size was not as impressive as in many reported cases either because the myxedema was mild because it had been present only a few months or because of other unrecognized factors

( ) Proc Staff Meet Mayo Clin 20 50-56 July 11 1945

The striking electrocardiographic changes sometimes seen were also absent. In most cases of myxedema with flattening or inver sion of all T waves probably the patients had h1 l the disease longer T waves in the patient s electrocardiograms showed no sig nificant difference Prolongation of the P R interval noted in the first and second tracings was not ev dent in the third and fourth. This delay in auriculoventricular conduction time was thought to be an effect of the myxedema Impaired ventricular conduction time remained the same in all tracings (QRS 0 1 second) and was probably due to hypertensive arteriosclerotic changes Unfortu natelv no electrocardiogram was made prior to development of myxedema.

Appearance of myxedema and its subsequent control did not accelerate the degenerative changes attributable to the patient s age and hypertension namely left ven tricular hypertrophy bundle branch block and grade 1 to 2 narrowing of the retinal arteries

PSYCHONEUROSIS

Psychosomatic Disorders As Revealed by 13 000 000 Examinations of S lective Service Registrants Leonard G Rowntree[3] (M C U S A) believes that disease has two components—physical and mental—both of which must be properly evaluated in considering pathogenesis diagnosis prognosis prevention and cure of many diseases Selective Service can contribute definite information on the incidence of psychosomatic diseases The size and composition of the 4F pool (see Table) fur nishes a much needed perspective This pool grew stead ily at a rate of approximately 85 000 a month despite drastic lowering of standards including induction of limited numbers of men with uncomplicated venereal disease hernia and illiteracy and large numbers with dental defects

Age distribution is 1 400 000 under 26 approximately 700 000 between 26 and 30 and 1 400 000 between 30 and 38 Above 38 few can qualify and serve satisfac torily the rejection rate is over 60 per cent and the discharge rate unusually high

(3) Psy hosom Med. 7 7 30 J ary 194

Rejections included 601 300 (15 7 per cent) for mental disease (excludin, illiteracy), 536,200 (14 per cent) for mental deficiency (including illiteracy), and 200,900

ESTIMATED PRINCIPAL CAUSES FOR REJECTION OF REGISTRANTS 18–37 YRS OF AGE IN CLASS 4F AS OF APR 1 1944 (PRELIMINARY)

PRINCIPAL CAUSE FOR REJECTION	NO	%
Manifestly disqualifying defects	403 100	10 5
Mental disease	601 00	15 7
Mental deficiency	5 6 200	14 0
Physical defects	2 242 500	58 4
Syphilis	288 800	7 5
Musculoskeletal	287 500	7.5
Cardiovascular	246 800	6 4
Hernia	217 ,00	5 7
Neurologic	200 900	5
Eyes	197 °00	5 1
Ears	148 000	3 9
Tuberculosis	100 800	° 6
Lungs	65 600	1 7
Feet	48 800	1 3
Abdominal viscera	4(900	1
Kidney and urinary	39 000	1 0
Varicose veins	38 400	1 0
Genitalia	38 100	1 0
Endocrine	37 100	1 0
Teeth	,5 400	0 9
Skin	23 400	0 6
Neoplasms	23 400	0 6
No e	23 100	0 6
Gonorrhea and other venereal diseases	18 000	0 5
Hemorrhoids	15 500	0 4
Mouth and gums.	10 800	0 3
Infectious and parasitic	4 000	0 1
Throat	3 800	0 1
Blood and blood forming	3 600	0 1
Underweight overweight and other	79 ,00	2 1
Nonmedical	5° 000	1 4
Total	3 836 000	100 0

Includes reg trants r je ted for educat n l def n y b f e June 1 1943 and for fa lure to me t minimum intell g n sta dard aft r th t date, as well as those rejected for mental deficiency

(5 2 per cent) for neurologic disorders In May, 1944 discharges from the fighting forces numbered more than 500 000 Over a third of the rejections and over 40 per cent of discharges are for neuropsychiatric reasons

The question arises whether psychosomatic diseases should be included in the category of neuropsychiatric diseases Certainly they are closely related representing visceral expression of disease functional or organic in nature rather than nervous and mental diseases per se

A comparison of incidence and rejection rates for selected psychosomatic diseases during peacetime and for November and December 1943 shows the following facts Incidence and rejection rates for asthma nearly doubled for the total group and for whites and Negroes also Peptic ulcer increased nearly 50 per cent for both total incidence and rejection rates with the increase relatively greater for the Negro—2½ times that of peacetime rejections. History of peptic ulcer increased still more to three times that reported previously with the increase preponderantly in whites Gastro-intestinal syndromes increased 2½ times Neurocirculatory asthenia also more than doubled for the group but increased five times in the Negro although since many cases of tachycardia and transient hypertension may have been included in the later series the greater figures may represent something other than actual increase

This evidence of marked increase of incidence of psychosomatic diseases may represent the influence of war stress and strain and somewhat the desire of some registrants to avoid service The most striking finding is the increased incidence of psychosomatic disease in the Negro who in peacetime appeared to be relatively immune

Although psychosomatic medicine is in the limelight and its importance is being better understood the pictures presented are still indistinct and the part played by psychic factors lacks definition

Studies such as those carried out by the cardiologists [1944 YEAR BOOK OF GENERAL MEDICINE p 562—Ed] are urgently needed They re examined 4 994 rejectees to orient themselves and medical examiners of local boards and induction stations They corrected the errone

ous impression that incidence of functional heart diseases is greatly increased and that organic disease of the heart is relatively uncommon In cardiovascular rejectees rheumatic heart disease valvular lesions and myocardial involvement are still responsible for approximately 50 per cent of rejections They found neurocirculatory asthenia synonymous with effort syndrome disordered action of the heart and determined that it was closely related to if not dependent on psychoneurosis Studies of this kind are greatly needed in several psychosomatic disorders

RHEUMATIC FEVER

Public Health Aspects of Rheumatic Fever John R Paul[4] (Yale Univ) observes that the best evidence of a close relationship of rheumatic fever and streptococcic infection is that although epidemics of streptococcic sore throat tonsillitis and scarlet fever are followed irregularly by groups of cases or even epidemics of rheumatic fever the reverse is always true namely, all epidemics of rheumatic fever are preceded by epidemics of streptococcic disease In addition, rheumatic fever can be prevented in certain carefully controlled clinic populations and in institutions for children by daily administration of prophylactic doses of sulfanilamide or sulfadiazine Until reports of recent studies are available it seems unwise to discuss this prophylactic measure in the light of civil practice

From the seasonal standpoint prevalence curves in New England at least follow one another closely and it appears that a good year for streptococcic diseases such as tonsillitis and scarlet fever is a good year also for rheumatic fever Although rheumatic fever probably has worldwide distribution it is enormously more common in certain areas than in others particularly in the temperate zones where there are likely to be fairly long periods of inclement weather during which people tend to herd together withindoors The northern half of the

(4) Rhode Island M J 8 15 17 January 1945

United States and the Rocky Mountain area represent rheumatic fever areas

Diagnosis of rheumatic fever is vague and there is resulting confusion in data on incidence prevalence and general importance In Scandinavian countries where rheumatic fever is reportable incidence per annum has ranged from about 1 to 3 per 1 000 population Mortality statistics in the United States show that juvenile deaths (ages 5–24) from cardiac disease have averaged 17 per 100 000 population Active cases of rheumatic fever constitute 0 1–5 per cent of medical admissions in general hospitals About twice this figure may apply to children s hospitals Rheumatic heart disease has been detected among school children at the rate of 0 3–4 per cent and among college students 0 6–1 per cent These figures indicate roughly the general frequency and importance of the disease In the northern half of the United States it would seem to rank among the chronic infections next to tuberculosis and syphilis in importance

The period of midchildhood is that of greatest vulnerability to first attacks Although susceptibility to both first and recurrent attacks declines rapidly after puberty rheumatic fever is common during adolescence and young adult life and medical problems which arise from both active and inactive disease are equally common during the third and fourth decades In young and midadult life rheumatic heart disease is more significant than usually suspected for with advent of early arteriosclerosis an adequately functioning rheumatic heart may decompensate There is uncertainty regarding racial susceptibility or resistance because data are generally unreliable but Irish people living in the New York City area seem to acquire rheumatic fever somewhat more readily than the average population Negroes do not seem to acquire the disease more readily than whites but their mortality rate from rheumatic fever is higher

Living and home conditions as well as climate and

season, exert a profound influence, either directly or indirectly Rheumatic fever may be designated as a disease of late winter and early spring and as a disease of the slums It is acquired at a higher rate in cities than in rural areas and is more prevalent among urban people subjected to the most crowding There is the old story of "rheumatic streets and houses", if these exist it is here that work on control of air borne or contact disease should be directed The work of Army commissions which has disclosed much regarding spread of streptococci through sleeping and living quarters should eventually find application here in civil life

Studies of rheumatic families offer suggestive evidence that the tendency to acquire rheumatic fever is inherited similar to that which seems to exist in tuberculosis In a large family three or four children may be found to have advanced rheumatic heart disease and in such homes generally familiar to social workers in a Children s Cardiac Clinic public health measures should logically find their way

In development of public health programs emphasis has been placed on (1) necessary education for physicians, nurses and medical social workers and recognition that basically rheumatic fever stems from an infectious disease (2) necessity for better diagnosis and (3) provision of care for those already suffering from the disease There is no use giving the public the idea that much is to be done about rheumatic fever without backing it up with therapeutic facilities There is far smaller provision for bed care particularly long term than is adequate to meet the needs of any good public health program This should include both medical and nursing care during acute and subacute stages the latter requires special types of hospitals or homes and must be available to some patients for months or even a year or more During this period protection from hemolytic streptococcic respiratory infection should be carefully considered Provision for after care or follow up during inactive

phase of the disease is also essential to a good program

[I am sure Dr Paul will agree that training and placement in industry have an important part in this rheumatic heart picture — Ed]

Public Health Aspect of Rheumatic Fever Esley J Kirk (Omaha) states that the incidence of rheumatic fever easily ranks with that of other important diseases such as tuberculosis syphilis and poliomyelitis If all ages are considered rheumatic fever ranks third as a chronic infectious disease exceeded only by tuberculosis and syphilis However in individuals under 20 rheumatic fever causes more deaths than pulmonary tuberculosis and more deaths than pertussis measles meningitis (meningococcus) diphtheria scarlet fever and poliomyelitis combined Yet the program and funds for prevention and treatment of rheumatic fever are insignificant as compared with those even for poliomyelitis It is of utmost importance that the medical profession become better acquainted with incidence morbidity rate etiologic factors prevention early recognition and management of rheumatic fever and that its members assume responsibility for appropriate programs for its control

Community Organization for Control of Rheumatic Fever Donald B Armstrong and George M Wheatley[6] (Metropolitan Life Insurance Co) state that between 5 and 19 years rheumatic fever is among diseases the leading cause of death It is responsible for a large fraction of cardiac deaths and for heart disease which completely incapacitates or hampers the economic productivity of thousands in their prime years In draft examinations in New York City in 1940–41 heart disease was a cause of rejection in over 40 per 1 000 selectees

Epidemiologic studies show a high correlation between recurrence of rheumatic fever and such factors as crowded unhygienic living conditions and poor nutrition The disease also tends to be concentrated in certain fami

(5) N b k M J 30 165 166 M y 194
(6) N w Yo k State J Med. 45 169 173 J 15 194

lies and may also be influenced by psychologic factors Perhaps the most important factor in precipitating attacks is streptococcus The promising use of sulfonamides to prevent recurrences is giving new impetus to preventive efforts

Application of this knowledge requires mobilization and organization of community resources Rheumatic fever like tuberculosis cannot be successfully attacked by the medical profession alone or from one angle alone Expert diagnostic service must be made available to assist the practicing physician and to encourage reporting of the disease Tendency of the disease to recur demands that plans be developed to educate parents teachers, social workers and others in daily association with the child not only in good child health care includin periodic medical supervision but in recognition of manifestations of rheumatic activity Prolonged and expensive care usually necessary during active and convalescent stages of rheumatic fever implies that such care i often a community responsibility Crippling effect of rheumatic heart disease suggests the importance of occupational guidance in certain cases To meet these complicated needs organized medicosocial effort is necessary and this can best be stimulated by physicians

Incidence of Heart Disease and Rheumatic Fever in School Children in Three Climatically Different California Communities John J Sampson Paul T Hahman (M C A U S) Wilton L Halverson and Margery C Shearer[7] surveyed school populations in three communities with markedly different climates (Fig 81) for incidence of heart disease rheumatic fever functional heart murmurs and hypertension by a single skilled physician, using a uniform technic and uniform diagnostic criteria (see Table) One of these communities wa previously surveyed by another physician who used approximately the same technic and criteria

Rheumatic fever and rheumatic heart disease occur in

(7) Am Heart J 9 178 204 February 1945

SUMMARY OF 1939 AND 1940–41 SURVEYS IN REDLANDS, EUREKA AND SUSANVILLE, CALIF

		Total	Normal without Murmur	Normal with Functional Murmur	Normal Total	Unclassified	Congenital Heart Disease	Potential Rheumatic Heart Disease	Rheumatic Heart Disease	Total Rheumatic Cases	Total Organic Heart Disease
All children examined	Cases	6 ?49	4 9	1 030	6 008	77	43	38	81	119	1?4
	%	100	79 5	16 6	96 1	1 °	7–	6+	1 3	1 9	2
1939 Redlands and 1940–41 Redlands Eureka and Susanville	Cases	5 80	4 664	938	5 602	64	38	0	68	98	106
	%	100	80	16 1	96 1	1 1	65	5	1 17	1 7	1 8
1940–41 Redlands Eureka and Susanville	Cases	3 790	? 7/9	835	3 614	63	5	6	??	88	87
	%	100	73		95	1 0	66	68	1 63	? 3?	2 9

E l d g 447 c s w th o h st ri s o t hil h d r e de e f t y rs in th mmu ity
† Rhe m ti hi t ry po t e 22 (0 58 p ent) negati e 40 (1 06 p r t)

the warm dry climate of Redlands in a degree comparable to that in cities with mild temperate climates such as Cincinnati and San Francisco Susanville a mountain community with average humidity and precipitation but

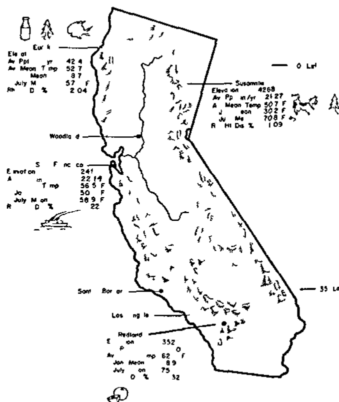


FIG 81 —M p f C l f h w g app o t lo at of tow

with wide extremes of average winter and summer temperatures presented a high incidence of rheumatic fever and rheumatic heart disease comparable to the incidence in the northeastern United States and Great Britain Eureka with a uniformly cool climate and high precipitation presented an unusually high incidence

Congenital heart lesions were found in greater frequency than in all previous surveys except those reported previously from other California communities Children with rheumatic valvulitis gave fewer past and family histories of rheumatic fever than did those in other reports

Certain statistical relations seem to exist between rheumatic disease and age sex race and housing There are questionable relations to diet and to a history of scarlet fever No definite relation of functional murmurs to any physical symptomatic or environmental influences such as age shape of chest or nutritional state was found in this survey

Experiences with Rheumatic Fever in the Army Irving S Wright[8] (M C A U S) states that rheumatic fever as it occurs in the Army is a manifestation of a highly communicable disease complex frequently preceded by an outbreak of upper respiratory infections Evidence is accumulating that it is an anaphylactic reaction probably to streptococcus group A It may be widespread in its attack on well nourished young men believed to be in excellent physical condition The greatest involvement has been among younger groups of service men Fatigue exposure to cold and dampness and close living quarters are believed to be important environmental factors Patients with a previous history of rheumatic fever are especially susceptible to recurrences when exposed to the rigors of military life

Incidence of chorea has been remarkably low Characteristic joint changes varied greatly in shifting tendencies and severity Cardiac manifestations included precordial discomfort tenderness on pressure pain dyspnea tachycardia premature contractions fibrillation and flutter Heart block varied from partial to complete with ventricular rates as low as 20 per minute Pericarditis occurred frequently enough to merit constant consideration Heart failure was rare during the first at

(8) B ll New Y k A d. M d 21 419 43 A gu t 1945

tae] Abdominal symptoms may represent onset of rheumatic fever Pain tenderness, rebound tenderness and cramps often cause confusion with appendicitis Subcutaneous nodules occurred only four times in over 1 000 cases Purpura has been rare Cerebral manifestations were seen in eight cases There were seven deaths two associated with pericarditis and five with heart failure All these patients had had previous attacks of rheumatic fever Four of the five with heart failure had pneumonia which in two pathologically resembled rheumatic pneumonitis Numerous other patients had what was diagnosed as primary atypical pneumonia but was probably in some cases rheumatic pneumonitis

The most consistent electrocardiographic change was prolongation of the P R interval—the longest being 0 6? This finding is often the only evidence of heart involvement and is usually transient disappearing in one to six months Partial auriculoventricular heart block with the Wenckebach phenomenon and dropped beats occurred in 6 per cent of cases Auricular ventricular dissociation occurred with equal frequency Prolongation of the P R interval was found in 15 of 200 patients who had what was considered typical rheumatoid arthritis Aschoff bodies have been found in hearts of many persons who died after years of so called typical rheumatoid arthritis The prolonged P R intervals added additional evidence to the hypothesis that these diseases often are closely related or run concurrently in susceptible individuals

In eight questionable cases of rheumatic fever with normal electrocardiographic findings six showed significant disturbances in rhythm usually associated with rheumatic fever after injection of 0 5 mg ergotamine tartrate There was first degree auriculoventricular heart block in four second degree block with dropped beats in one and nodal rhythm with first degree block in another Maximal effect was noted in 30 minutes and usually disappeared in 60 minutes In five individuals

rechecked after the active phase had subsided no altera tions from normal except for slight slowing of sinus rate could be produced by the same experiment If this work is substantiated by further studies it offers a more sensitive technic for detection of cardiac involvement in rheumatic fever

Present status of treatment remains unsatisfactory Penicillin and sulfonamides have proved valueless and there is no evidence that penicillin is a preventive Prolonged daily dosage of sulfanilamide apparently lessens frequency of recurrences There is suggestive evidence that short courses of sulfonamides are of long term value in prophylaxis of primary or recurrent attacks of rheu matic fever Incidence of upper respiratory infections especially those associated with certain strains of strep tococci can be markedly reduced by this practice

Treatment of rheumatic fever has been advanced with development of a method for determining the level of salicylates in the blood thus aiding in control of dosage It is fairly well agreed that large doses of sodium salicyl ate i e 10 Gm or more daily are more rapidly palliative than the former smaller doses It is highly doubtful that intravenous administration of salicylates is of greater value than oral administration Clinical response to large doses has been rapid but response of sedimentation rate has in many cases been slow Use of massive dose methods does not offer complete protection against pericarditis myocarditis or endocarditis

With massive doses salicylism must be watched for It can be prevented by giving sodium bicarbonate with sodium salicylate but this also lowers the blood level of the salicylate The effect which this may have on effi ciency of the salicylates has not been established

Prevention of Streptococcic Upper Respiratory In fections and Rheumatic Recurrences in Rheumatic Chil dren by Prophylactic Use of Sulfanilamide Ann G Kuttner[9] (Irvington on Hudson N Y) reports that at

(9) Mod Co pt C d sc l Dis l 12 n 10 O t ber 1943

Irvington House a sanatorium for rheumatic children aged 7–15 during two successive winters patients were divided into two groups matched as closely as possible in regard to age sex number of previous rheumatic attacks and cardiac findings One group received small doses of sulfanilamide and the other served as control Weekly leukocyte counts and bimonthly hemoglobin determinations were done on all children receiving sulfanilamide and sulfanilamide blood levels were determined every three weeks During both years the contrast in incidence of streptococcic upper respiratory infections and rheumatic relapses in treated and untreated groups was striking Only 2 of 108 children receiving sulfanilamide contracted streptococcic pharyngitis, and in only 1 of these did rheumatic manifestations develop Of 104 controls 48 contracted streptococcic pharyngitis, in 23 of these definite rheumatic relapses developed and 5 additional children had laboratory evidence of mild clinical symptoms suggesting rheumatic activity No rheumatic recurrences were observed in children who escaped streptococcic upper respiratory infections

Treatment of Rheumatic Fever Geo C Griffith, W H Leake and Hugh Butt[1] (M C U S N R) claim that disabling heart disease could be avoided if the fulminating polycyclic type could be attenuated and shortened and if the monocyclic and subclinical types could be prevented from causing severe vascular tissue reactions

Since every patient with acute hemolytic streptococcic sore throat is a potential subject he should be observed for a long period to recognize if possible the earliest stage of active rheumatic fever and then be placed on a planned regime

Absolute rest in bed is essential and should be continued until signs of activity have disappeared At least 3 500 calories should be given daily, the nature of the food depending on the patient s general condition

Salicylates relieve pain have an analgesic and anti

(1) Mod Co cepts C d a cul r D l 24 p 6 Jun 1945

pyretic action and increase the ab orption of the trans udate in serous cavities but have no effect on the course They do not prevent recurrences and have little if any analgesic and antipyretic effect in the second and third cycles or in the course of the prolonged monocyclic cases

Sodium salicylate 25 gr and sodium bicarbonate 10 gr every four hours or aspirin 20 gr and sodium bicarbonate 20 gr every four hours day and night, with 3 000 cc water will give the optimum blood level of 30–50 mg per cent in 24–48 hours Enteric coated tablets should never be given because with their slow disintegration in the colon a toxic dose may suddenly be absorbed from the accumulated tablets

The dosage used rarely produces symptoms of salicyl ism Salicylism in ambulant patients is quickly relieved by return to rest Large amounts of water and food will prevent gastric irritation

Intravenous administration is indicated only when salicylates cannot be given orally Salicylates do not help much in congestive failure Given by rectum there is poor absorption therefore oral administration is the method of choice

Digitalis has doubtful value in the active stage being indicated only with onset of congestive failure during active carditis It is given in full dosage orally 1 U S P unit per 10 lb body weight adding 1 unit (1½ gr) for each additional day required to complete digitalization which is then maintained by 1 unit daily Digitalis or quinidine is not used in the rare instances of paroxysmal auricular fibrillation and paroxysmal tachycardias which subside with rest Congestive failure rarely occurs in the quiescent stage Quinidine does not prevent premature contractions in the acute stage but rest and avoidance of cigarets are of distinct value In rheumatic pneumo nitis and congestive failure oxygen is of great value relieving restlessness cyanosis dyspnea and tachycardia It is given early and as long as necessary by nasal tube at about 4 L per minute through a humidifier

A total of 46 of 240 unselected patients were treated with sulfonamides at onset of rheumatic fever Of these 4 had a good response and 20 none the condition was worse in 11 and there was no comment in 11 cases Patients with intercurrent tonsillitis sinusitis or otitis media with positive hemolytic streptococcic cultures were treated with sulfadiazine and salicylates at the same time

Recurrence of rheumatic activity was rare Therefore in treatment of rheumatic fever per se the authors believe sulfonamides are contraindicated

Salicylate Therapy in Rheumatic Fever in Children Leo M Taran and Martin H Jacobs (Kings County Hosp) studied effects of massive salicylate therapy in 64 children 6–14 observed during an acute rheumatic episode Of those with rheumatic polyarthritis seven received salicylates intravenously and seven received massive oral doses In the group with rheumatic carditis, two children with a severe form received sodium salicylates intravenously six received massive doses of sodium salicylate orally at onset of an attack, six received massive doses orally beginning several weeks after onset of carditis five received the usual small doses of sodium salicylate at onset and 10 some weeks after onset of the rheumatic episode Twenty one children with rheumatic carditis did not receive any salicylates but were treated by complete bed rest nursing care and symptomatic measures

Results indicate that rheumatic polyarthritis responds promptly to large doses of salicylates (sufficient to raise the plasma salicylate level to 350–450 gammas per cc) administered either orally or intravenously The intravenous route apparently offers no significant advantages over the oral route provided the same plasma salicylate level is reached No difficulty was encountered in reaching the desired level with oral administration Technical difficulties and annoying symptoms with the intravenous

( ) J Pedi t 27 59 68 July 1945

method outweigh possible benefits of slightly more prompt results There were no thrombopenic disturbances and no detectable evidence of acidosis in these patients

Massive doses of salicylates in rheumatic carditis apparently produce equally effective results Sedimentation rate returns to normal as promptly as in the polyarthritic group provided therapy is instituted at onset of rheumatic activity When treatment is postponed subsidence of the rheumatic process is delayed many weeks All other signs of carditis however subsided simultaneously with return of sedimentation rate to normal Intravenous therapy in this group may be hazardous

Small doses of salicylates apparently do not affect the course of rheumatic carditis The course seems to be the same whether insufficient doses are given or therapy is completely withheld Duration of the active process as measured by presence of an elevated sedimentation rate is much longer than in the group receiving massive doses Furthermore when salicylates are withheld or given in small doses the rheumatic process shows evidence of activity for a long period following return of sedimentation rate to normal

Evaluation of a therapeutic agent for rheumatic disease is difficult because suppression of the sedimentation rate does not always signify cessation of the rheumatic process Subsidence of all clinical and laboratory evidence of rheumatic disease without detectable change in cardiac status does not always forestall the advent of significant heart disease years later without obvious recurrence of rheumatic active disease While it cannot be definitely stated that massive salicylate therapy unequivocally suppresses the rheumatic process and prevents the stigmas of heart disease this treatment does make the patient symptom free

Massive salicylate therapy may occasionally present definite hazards particularly on intravenous administration in rheumatic carditis Hence its use should be reserved for experienced investigators More data must

be presented to show the effect of a rapid rise of plasma salicylate level on liver metabolism its possible injurious effects and methods for neutralizing these effects before the method is proposed for general use

Syphilis

Diagnostic Difficulties in Uncomplicated Syphilitic Aortitis with Note on Roentgenkymography of the Aorta Samuel H. Averbuck[3] studied 47 patients with positive serologic evidence of syphilis to determine cardiovascular status The group included men and women of all ages Some had acquired their infections comparatively recently while others gave a history of long standing infection All had been receiving antisyphilitic therapy for varying periods None presented symptoms or signs of outspoken or advanced cardiovascular syphilis such as aneurysm aortic insufficiency or narrowing of the coronary artery orifice exclusion of such cases was intentional for they present no exceptionally difficult diagnostic problem Signs or symptoms that would justify diagnosis of uncomplicated syphilitic aortitis were particularly sought Criteria of the Co operative Clinical Group with modifications suggested by Maynard and his co workers were used as guides In addition to careful questioning and examination each patient was studied by fluoroscopy of the chest electrocardiography, and roentgenkymography of the aorta In only 2 cases was diagnosis of uncomplicated syphilitic aortitis warranted It was recognized that in the light of the higher incidence of syphilitic aortitis (60–80 per cent) reported in autopsy studies of syphilitics many cases of specific aortitis in this series were undetected Roentgenkymography of the aorta gave no assistance Difficulty of establishing normal standards of visualized aortic pulsation made interpretation impossible Many factors made determination of a normal kymogram of the aorta at different age periods etc difficult Similar obstacles sur

(3) J Mt Sin Hosp 12 41 5 May-Jun 1945

round establishment of normal limits for dimensions of the aorta when studied fluoroscopically or roentgenologically

It is concluded that early syphilitic aortitis before occurrence of coronary artery orifice involvement aortic insufficiency or aortic aneurysm, is clinically undetectable Exceptionally it may be diagnosed when specific signs are found in a young syphilitic patient who has neither arteriosclerosis nor hypertension

Trauma

Cardiac Trauma James G Carr[4] (Northwestern Univ) states that both penetrating and nonpenetrating injury may be present e g forcible trauma over the cardiac area may injure the heart and fracture one or several ribs which may easily add penetrating trauma Trauma may be incurred in sports traffic and industry Results of these accidents are many Pericarditis usually acute is frequent and severe there may be myocarditis with vascular damage or gross dilatation of the auricle ventricle or aorta Cardiac rupture or perforation of septum and valves may occur Valves may be badly torn Chronic infectious processes or aneurysm of the aorta or cardiac wall may develop

Symptoms suggestive of myocardial injury following direct trauma to the chest wall are oppression behind the sternum with pain tending to radiate into the left arm dyspnea and perhaps frothy expectoration Severe myocardial damage sometimes causes little distress and when the sternum or ribs are fractured symptoms of cardiac injury tend to be masked Transient electrocardiographic signs must be sought early Typical attacks of coronary thrombosis with characteristic electrocardiographic findings have been recorded

Tachycardia and various types of aberrant rhythm may develop Auricular fibrillation ectopic beats and ventricular auricular and nodal rhythms may occur

(4) W n M J 44 517 5 1 M 1945

Heart block of various degrees may develop Electrocardiographic evidence of trauma may present similar or identical features of occlusion, in another group electrocardiograms are abnormal but not characteristic

Alleged injurious stimuli relied on in legal claims for cardiac disability fall in four groups direct trauma to the heart including heavy impact injuries to the overlying thorax, indirect trauma due to excessive demands on an impaired heart usually consisting of some extraordinary lifting or straining not regarded as normal in that line of employment, exposure of the heart to noxious agents carried in the blood stream such as carbon monoxide or other poisons and injuries ascribed to psychosomatic stimuli consisting of nervous shock without substantial impact or of emotional upset or other psychic disturbance

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ANATOMIC DIAGNOSIS

Thrombosis of Coronary Arteries

Influence of Extrinsic Factors on the Coronary System N C Gilbert (Chicago) discusses the role of reflex actions in producing symptoms of heart disease and in advancing heart disease already present Normally, stimuli carried to the heart and its blood supply via the autonomic nervous system keep these organs balanced with the demand for a changing blood supply by the rest of the body occasionally however reflexes occur which are abnormal and disadvantageous to the heart or organ being served

That coronary sclerosis and narrowing are related to anginal pain is well known but frequently such pain cannot be explained on a basis of pathologic changes alone Even in patients in whom heart disease is confidently assumed such extrinsic factors as ingestion of food and inspiration of cold air may influence anginal pain and other conditions Anginal pain occurs after

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eating especially if the person walks soon after the meal but it may also occur while he is sitting quietly One reason for its occurrence is the increased demand on the heart during digestion The pain frequently disappears when gas is expelled from the stomach However this is not the final answer since the pain is not constant in the same person eating the same meals under similar circumstances

Distention of an animal s stomach with a balloon causes a decrease in coronary flow which does not follow when the vagi are cut or atropine is administered thus proving that the decreased flow is due to a reflex vasoconstriction of the coronary vessels When the cardiac end of the stomach at the esophageal hiatus was distended the response was greater as it was also on distention of the esophagus Similar results were noted in an unanesthetized animal carrying a Rein thermo strom uhr or after air distention of the free abdominal cavity

Anginal pain may occur when the abdomen is distended with gas and be relieved by expulsion of flatus. Such pain seen in some cases of hiatus hernia disappears when the defect is reduced following relief of the intra abdominal pressure Persons with known angina of effort after breathing mixtures low in oxygen content for a few minutes have anginal pain which is relieved immediately by switching to pure oxygen. When the test is made after a meal the pain comes on much sooner this effect is prevented by administration of atropine before the meal

Hiatus hernia and anginal pain are associated relieving the hernia reduces or eliminates the pain Bending over coughing lifting or anything which causes increased abdominal pressure will enlarge the hernia and induce attacks The recumbent position especially after a meal may start an attack which is relieved by standing up Electrocardiographic changes suggesting coronary disease may occur when the hernia is present and disappear when it is reduced

Diverticula of esophagus or duodenum and duodenal ulcers may reflexly cause anginal pain Gallbladder dis ease also causes such pain, and there is experimental evidence that distention of the gallbladder or cystic duct decreases coronary flow

Anginal attacks may be precipitated by breathing cold air or facing a cold wind Stimulation of nasal mucous membrane causes a reflex slowing of the pulse, stimulates the inhibitory vagus fibers and inhibits the tonic effect of the sympathetic fibers When a person known to suffer anginal pain breathed a mixture low in oxygen adminis tration of ergotamine tartrate caused the pain to occur much sooner Ergotamine tartrate may cause pain even when the patient is not breathing low oxygen mixtures

When one coronary artery is occluded, there is a reflex vasoconstriction of the other coronary vessels which greatly influences the mortality and sequelae of coronary occlusion It was demonstrated that occlusion of one coronary vessel caused reflex vasoconstriction of the other coronary vessels decreasing the blood supply to the uninfarcted tissue and that to the infarcted muscle through the anastomosing vessels Dissection of the vagi, administration of atropine or removal of the stellate and upper five thoracic ganglions will prevent the reflex vas oconstriction with resultant lowered mortality

Subcutaneous administration of atropine immediately after occlusion has occurred reduces mortality which can be further reduced by using aminophylline or papav erine with the atropine

Cardiovascular Diseases Some general considerations are presented by William D Stroud[6] (Philadelphia) Coronary thrombosis with myocardial infarction can exist without pain (of 100 patients 15 were without pain) but usually there are other signs such as dyspnea or increase in congestive failure

The patient with coronary thrombosis is usually told that he should lie flat and still without turning to either

(6) Kentucky M J 43 174 179 J ly 1945

side Stroud thinks the average person can have three or four pillows 24 hours after an infarction he can listen to the radio read and even have a few puffs from a cigaret if he has been used to smoking two packages a day These patients may also have two or three shots of alcohol a day it dilates the coronaries and that is the purpose for which aminophylline and various coronary dilators are prescribed

The average doctor with coronary disease stays in bed a shorter time curtails his activities much less and does all or most of the things he tells a patient in the same condition not to do Although most patients with coronary disease are told not to drive an automobile Stroud in 25 years experience has known of only one instance in which the person was unable to shut off the motor and pull over to the side that patient did not know that he had coronary disease since it was his first attack Coronary patients should be allowed to do as much as possible to bring happiness to them during their remaining years

Clinical Significance of Pain in Acute Coronary Occlusion with Myocardial Infarction Not all patients with coronary occlusion have pain nor do all react to the same disease similarly The individual hyposensitive to pain is likely to have more substitution symptoms In a study of 350 cases of coronary occlusion M A Kugel[7] (Miami Beach Fla) found *only* 10 without pain an incidence of less than 3 per cent Review of the literature reveals that all investigators who clearly define their criteria for pain and who have considered substitution symptoms as a manifestation of pain also found a low percentage of patients without pain

Although characteristic severe precordial pain may occur in coronary occlusion in many cases symptoms are atypical and pain is mild or in rare cases even absent In the hyposensitive individual pain may be manifested by substitution symptoms or when pain is absent presenting symptoms may be sudden dyspnea sudden in

(7) J Mt S al Hosp 12 422-438 May-June, 1945

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(6) Kentucky M J 43 174 179 July 1945

asked to exercise by jump ng on one foot while another tracing was taken He coll ipsed immediately and went into severe shock and was then first seen by an officer in the medical service who made a diagnosis of coronary thrombosis. Pulse was slow gallop rhythm was evident and blood pressure was 100/70 His condition was critical but under appropriate therapy he improved and eventually recovered Serial electrocardiographic tracings were characteristic of posterior wall infarction. Failure to recognize inter relation between effort and acute myocardial infarction in this case was a serious error

Quality of cardiac pain is mimicked by disease of other organs and therefore noncardiac disease is often mistakenly diagnosed Cardiac pain particularly of angina pectoris, characteristically appears during effort or emotional excitement and is relieved by rest Direct inquiry should be made regarding all attendant circumstances prior to the attack Much significant information not spontaneously volunteered by the patient will frequently be uncovered Appearance of distress on exertion or under emotional stress should indicate a tentative diagnosis of angina pectoris coronary failure or insufficiency or myocardial infarction until such diagnosis is clearly excluded on the basis of further evidence Sometimes persistent weakness is the sole finding and its significance may be corroborated only by progressive characteristic changes in later electrocardiographic tracings Other concomitant factors such as exposure to cold or eating which increase the work of the heart may superimpose their effect

Clinical criteria which must be satisfied to demonstrate a relationship of effort to acute myocardial infarction are (1) development and increase of cardiac symptoms such as pain or substernal distress during or immediately following unusual effort (2) continuation of symptoms after cessation of effort (3) presence of clinical signs and symptoms of acute myocardial infarction and (4) development of characteristic electrocardiographic pattern of acute anterior posterior or lateral wall myocardial infarction

Pathologic mechanisms which induce acute myocardial

crease in myocardial failure, vertigo syncope digestive disturbances or collapse

It is in the hyposensitive individual that the seriousness of the underlying condition is most likely to be overlooked One cannot depend on pain alone even when electrocardiograms seem characteristic for final diagnosis of acute coronary occlusion One must go into the history in great detail and consider the entire clinical picture

Relation of Effort to Attacks of Acute Myocardial Infarction Most military personnel must undertake strenuous effort to which some officers particularly from civilian life are unaccustomed It therefore might be anticipated that if effort and myocardial infarction are causally related an increased number of such cases might be witnessed in the Army Herrman L Blumgart[8] (MC A U S) selects from a much larger group 11 cases in which unequivocal electrocardiographic tracings of myocardial infarction were observed during life and/or an acute fresh occlusion of one of the three major coronary arteries was disclosed at autopsy In eight cases in which electrocardiographic tracings were made the changes were characteristic One of these patients died later and autopsy revealed a fresh thrombus in the left anterior coronary artery Of three patients who died before such tracings could be made autopsy disclosed fresh thrombosis of a coronary artery in two and fresh subintimal hemorrhage in the other

The question of relation of effort to acute myocardial infarction has considerable practical as well as theoretical importance Recognition of relation of effort to acute myocardial infarction may be of great importance in diagnosis and clinical management One illustrative case is given here

Captain 4" had precordial discomfort immediately after exercise in the gymnasium Despite considerable precordial discomfort during the night he did not seek medical advice until the following afternoon. Electrocardiographic tracings were equivocal and he was

(8) J A M A 128 775 778 July 14 1945

cerebral circulation in 7 in the femoral artery in 5 and in both cerebral and femoral arteries in 1 None of the 16 who received other treatment had fatal embolism in the systemic circulation In 36 patients without congestive failure digitalis alone produced no greater incidence of systemic embolism than did other types of treatment

According to these data the danger of giving digitalis in myocardial infarction was not that of inducing ventricular fibrillation and sudden death or of producing cardiac rupture nor in its administration to patients without congestive failure the danger was in administration to patients with the cardinal indications for digitalis those with congestive failure and auricular fibrillation

The hazard of giving digitalis apparently was chiefly that of embolism Embolism in the systemic circulation depends on presence of mural thrombi in the left side of the heart and on a mechanism that releases them The importance of pre existing mural thrombi in producing embolism and particularly the importance of duration of auricular fibrillation in producing the thrombi is suggested by the high incidence of fatal emboli in eight patients in whom auricular fibrillation had been known to exist before onset of myocardial infarction Of the seven who died five died of emboli in the greater circulation These five had been given digitalis alone and auricular fibrillation had persisted until death by embolism Effect of old age in relation to mural clots is evidenced by increased age average age was 70 Occurrence of systemic embolism was correlated also with time of persistence of arrhythmia following the attack of myocardial infarction Of 49 patients with auricular fibrillation persisting until death 36 died in seven days or less and 13 died after seven days or more of arrhythmia Of 36 dying in the first week only 7 died of systemic embolism whereas of 13 dying after seven days of arrhythmia 9 died of this cause

infarction during or soon after effort are (1) subintimal hemorrhages or rupture of an atheromatous abscess following strenuous effort and (2) occurrence of relative ischemia caused by strenuous effort and resulting in need for increased blood flow which the arteriosclerotic vessels are unable to meet

[Persistent weakness and easy fatigability, as suggested by Blumgart are among the most frequent early symptoms in impending coronary occlusion in those who do or do not have the usual angina of effort —Ed]

Is Digitalis Indicated in Myocardial Infarction? Theoretical dangers of digitalis in myocardial infarction are production of (1) ventricular fibrillation (2) rupture of the heart (3) embolization (the latter two supposedly due to the more powerful systole) or (4) coronary constriction

John Martin Askey and Otto Neurath[9] report effect of digitalis in 84 patients with auricular fibrillation, 48 of whom also had congestive failure found among 1 247 patients with myocardial infarction at Los Angeles County General Hospital Forty four patients received digitalis alone 40 received either quinidine alone quinidine and digitalis or no medication Apparently digitalis presented no greater hazard as to sudden death than other medication Three sudden deaths followed use of quinidine two patients had intraventricular block and one had prolonged atrioventricular conduction occurring prior to onset of auricular fibrillation Of 56 patients given digitalis alone or with quinidine rupture of the heart occurred in 3 of 17 patients receiving no medication rupture occurred in 1

Digitalization in most cases was fairly rapid averaging 24–30 gr powdered leaf in three to four days Of 32 patients with congestive failure receiving digitalis alone 31 died (96 8 per cent) of the 16 who received other treatment 11 died (68 7 per cent) Clinically recognized fatal embolism in the greater circulation occurred in 13 of the 31 who died after receiving digitalis alone in the

(9) J A M A 1 8 1016 1018 Aug 4 1945

anginal pains initiated by lessening degrees of effort or stress (2) appearance of anginal attacks during rest with preceding effort angina (3) true anginal pain re curring more or less rhythmically at lessening intervals or an unusually prolonged attack not responding to usual treatment

Acute coronary insufficiency may occur in a heart with damaged coronary vessels in circumstances causing rela tively prolonged myocardial ischemia which leads to ir reversible changes and consequent infarction These may be increased or prolonged by cardiac overload or acute coronary insufficiency may result from an acutely re duced coronary supply associated with hemorrhage shock dehydration or severe debilitating illness in a sub ject with coronary disease

Myocardial infarction rather than coronary occlusion which usually precedes it produces the symptoms and signs of the occlusion syndrome characterized by agon izing chest pain shock fever leukocytosis increased sedimentation rate lowered blood pressure and charac teristic electrocardiographic changes Prompt bedside recognition is imperative for assuring proper protective management Certain suggestive features favoring a posi tive diagnosis in a borderline case include a cardiovascu lar family tendency history of antecedent hypertension or diabetes or possession of a high strung temperament by a sedentary overnourished man

[The family h story is most important It is a rare patient who develops a coronary occlusion unless one of his parents has had a coronary occlusion o a cerebral vascular acc dent —Ed]

Thiouracil Treatment of Angina Pectoris Rationale and Results Wilhelm Raab[2] (Univ of Vermont) found thiouracil effective in 8 of 10 cases In four three of which were severe symptoms disappeared during treat ment When the drug was replaced by a placebo without the patient s knowledge partial or complete relapses occurred within weeks or months in these cases Definite improvement regarding frequency and intensity of an

(2) J A M A 1 3 49 56 M y 26 1945

Although the precise mechanism for production of increased embolism is not established these cases justify several conclusions Congestive failure occurring with auricular fibrillation and myocardial infarction was associated with a high incidence of mural thrombi (75 per cent) and risk of fatal embolism after digitalis administration alone was very high Digitalis apparently mobilized the *thrombi in a dangerously high percentage,* to such degree that the risk of the drug became greater than the risk of the condition itself Digitalis is particularly indicated in congestive failure of heart disease in general but from these results congestive failure of *auricular fibrillation occurring with myocardial infarction* is definitely not an indication for use of digitalis alone

[I cannot agree with this conclusion If I had a myocardial infarct with *auricular fibrillation* and even slight *evidence of congestive* failure I should want to be digitalized —Ed]

Practical Points in Recognition and Management of Coronary Disease are enumerated by O P J Falk[1] (St Louis Univ) Prompt relief of symptoms control of complications and improvement in recovery rate in acute coronary episodes are largely contingent upon prompt recognition of the earliest clinical expression of angina pectoris impending occlusion acute coronary insufficiency *or actual myocardial infarction*

Since the earliest expression of true angina pectoris is subjective accurate diagnosis may rest on history Constricting substernal pain or pressure sense or pain in the lower chest or epigastrium radiating to the left shoulder or arm brought on by physical effort or emotional stress is likely to be due to angina pectoris particularly when relieved *promptly* by rest or nitrites A precordial ache or sticking pain not directly related to effort is often attributable to chronic fatigue or anxiety states excessive smoking or digestive disorders

Three situations especially suggest imminence of complete closure after coronary narrowing (1) history of

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(2) J A M A 1 8 49 56 M y 6 1945

ginal symptoms occurred in three cases in one placebo administration led to partial relapse One patient was only slightly improved, but two subsequent series of roentgen irradiations of the adrenal region almost eliminated symptoms Two patients with severe angina pectoris died of coronary occlusion during treatment without having experienced improvement

Based on this experience adequate dosage appears to be 0 4 Gm daily for a few weeks or months, then 0 2 or 0 1 Gm over longer periods and eventual tentative discontinuance Doses over 0 6 Gm daily should be avoided in view of reported side effects Onset of subjective improvement was reported after 10 days to 6 weeks If thiouracil was given in a second or third period following placebo induced relapses improvement and disappearance of symptoms occurred more rapidly A significant decrease of basal metabolic rate was observed in the seven decidedly or completely improved patients rather closely paralleling diminution or disappearance of anginal symptoms No significant lowering of basal metabolic rate occurred in the two patients who died and only a moderate and temporary fall was observed in one patient who was only slightly improved Maximal improvement was reached when basal metabolic rate had fallen 7–27 points below its original level Relapses occurred simultaneously with return of basal metabolic rate toward pretreatment level Initial basal metabolic rate at the beginning of thiouracil treatment had no apparent influence on results

Fully developed myxedema resulted in one case, in four there was some puffiness of the face in two combined with sleepiness when basal metabolic rate was lowest These phenomena disappeared spontaneously one or two weeks after discontinuation or reduction of thiouracil medication Blood cholesterol was elevated during the hypothyroid episodes

The only fact which can be concluded from the approximate parallelism of changes in basal metabolic rate

and symptomatic response is the fundamental involvement of even the normal thyroid function in the mechanism of a probably large group of angina pectoris cases That this involvement consists essentially of sensitization of the heart muscle to the anoxiating action of epinephrine and probably also of sympathin originating in the heart itself is suggested by many clinical and experimental facts

Therapeutic efficacy of thiouracil in angina pectoris suggests that it is a valuable and preferable substitute for thyroidectomy and constitutes a further step in clarification of the pathogenesis of angina pectoris as a phenomenon of hormonal chemical interference in myocardial metabolism All prolonged therapeutic successes achieved in angina pectoris by therapeutic measures influencing the endocrine system can be explained as due to diminution of the acutely anoxiating effect of epinephrine and sympathin on the myocardium whose blood supply is curtailed by coronary sclerosis

[At present thioura l should be used w th great caution It is a powerful drug —Ed]

Myocardial Infarction T E Lowe (Univ of Melbourne) and W B Wartman[3] (Western Reserve Univ) believe that correlation of anatomy and physiology of the heart with diseases of the coronary arteries explains many of the indications of the existence of an infarct Fall of arterial blood pressure is usually due to the amount of muscle tissue destroyed or to the particular muscle concerned Rhythmic abnormalities and electrocardiographic changes will be better understood when sufficient data are compiled concerning the electric activity of the heart Rupture of ventricles or oncoming congestive cardiac failure may perhaps be predictable on the basis of accurate localization of the specific muscle bundles involved

Surgery for improving myocardial blood supply requires knowledge of the behavior of the diseased coronary vessels Such surgery aims at creating new anas

(3) Brit H rt J 6 115 128 J ly 1944

tomoses between extracardiac and cardiac vessels From these procedures one assumes that the arterial pressure gradient will force blood from one to the other however, that such a gradient will exist is not guaranteed In cases

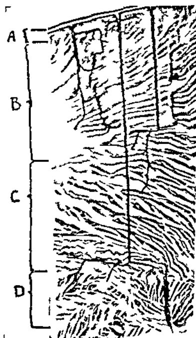


FIG 8 —S t on th gh l ft ventr l near base sh ws fou muscle layers A per a d al p rt o f sup rfi al layer B nd C tw deep m les D e d ard al port on f superfi al laye Pecul a a r ng me t of muscular b n h f o ary t es by wh h pare t rt ry g e branche to perica dial and endoc rdi l portions f superfici l muscle but not to deep mus le between

suitable for surgery the deficiency in blood supply frequently exists deep in the ventricular wall Therefore it is doubtful that a satisfactory gradient will exist to transfer any amount of blood to the heart, and it is possible that the flow will be in the opposite direction The variable results following these procedures probably are due to this unpredictable factor

Coronary Occlusion in Industry Large industries have been reluctant to employ persons with arterio sclerotic heart disease or those who have had myocardial infarction Eugene B Levine and Edward Phillips[4] (Permanente Found Hosp) state that coronary occlusion with myocardial infarction should not of itself disqualify a man seeking employment even in heavy industry Employers must be safeguarded but it is as important that the individual recovered from myocardial infarction be returned to a useful and productive life Unless the illness impairs production value the person should not become dependent because of the illness



F G 83 —Sect f d sc d g m f l ft o y rt ry h w g ma ked t g rt ri l d ec t thrombo s l pp tly h lthy m 3 l h se t th mech al b k t th es l, b t th at f e t f bl d fl w d st t f ll t l e c l t e mp rt t g d th (L we-W rtm p 613)

Eighty four persons with 97 infarcts were studied No cases of infarction developing after Dec 31 1943 were included Diagnosis was established by electrocardiogram and study of the history The period of observation terminated Apr 20 1944

(4) Am H rt J 29 588 594 M y 1945

tomoses between extracardiac and cardiac vessels From these procedures one assumes that the arterial pressure gradient will force blood from one to the other however, that such a gradient will exist is not guaranteed In cases

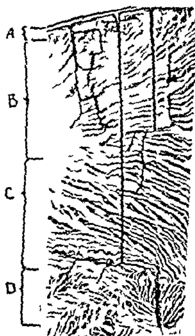


FIG 8 — S ct n tl gh l ft e tr l n h se h s f ur muscl layer A per d l p t f p fl al l B d C tw de p muscl D nd a l g t f p fi al layer Fe ul ar rr ng ment of mus ul r br h f y t e by ul h p t y g s bran h s to per ard al a d e l ital p rt n f s p fi al mu le but not t d p mu le betw n

suitable for surgery the deficiency in blood supply frequently exists deep in the ventricular wall Therefore it is doubtful that a satisfactory gradient will exist to transfer any amount of blood to the heart and it is possible that the flow will be in the opposite direction The variable results following these procedures probably are due to this unpredictable factor

and normal activity can be resumed with mild or even moderate discomfort

It is expected that some of the unemployed patients will return to work while some of those now working will stop Not every employed person who survives a coronary occlusion will be able to work but many ap parently recover sufficiently to continue in the same or lighter work without symptoms or fear of shortening life or precipitating another infarction

Ample time should be allowed for a full recovery and scar formation Patients who are symptomatically well enough should be returned to work under medical super vision. The work to be done is limited by the cardiac reserve It is the physician s responsibility to return the convalescing patient to an independent productive life if possible However it would be unwise to assign such a person to a job in which sudden collapse would endan ger the lives of others

[In my opinion too few persons with coronary occlusion are al lowed to return to their former jobs or if they continue to have signs of coronary insufficiency to jobs with less emotional and physical stra n —Ed]

Prognostic Significance of Auricular Fibrillation in Association with Myocardial Infarction John Martin Askey (Los Angeles) and Otto Neurath[5] (M C A U S) state that of 1 247 patients with myocardial infarction 84 had auricular fibrillation (7 7 per cent) In 29 the arrhythmia disappeared and in 55 it persisted Of the 1 247 patients 642 (51 5 per cent) died The death rate among the 84 patients with auricular fibrillation was definitely higher (79 8 per cent) Among the 29 in whom the arrhythmia disappeared mortality was only slightly increased (58 6 per cent) whereas among those in whom arrhythmia persisted it was markedly increased (89 4 per cent) Persistence of auricular fibrillation was found to be correlated with both time of onset of the arrhyth mia and degree of pre existing cardiac damage The ar rhythmia persisted in nearly all cases in which it pre

(5) Am Heart J 29 575 580 May 1945

Average period of observation after infarction was 11 7 months Sixty five persons (75 per cent) performed manual labor and 19 (25 per cent) did light or sedentary work Fourteen patients died during the period of study nine dying immediately (within four weeks of infarction) Only 20 patients made complete symptomatic recovery Twenty three had subsequent angina pectoris 12 congestive failure, 13 mild angina pectoris with congestive failure 1 complete auriculoventricular block and 1 cerebral thrombosis Of the 70 survivors, 30 were working Those who made complete recovery included 10 working and 10 not working, 9 of the latter being unemployed because of personal reasons or unrelated illness Of the 10 returning to work 7 returned to the same work and 3 to lighter employment

Of the 23 patients with angina pectoris alone 11 were working at the end of the observation period Those not employed, however did not work because of the angina pectoris Among those with congestive failure, 2 were employed and 10 were not suggesting that congestive failure after myocardial infarction is more disabling than angina pectoris Of the 13 patients with mild angina pectoris and congestive failure 7 were working

Of the 30 persons working at the end of the observation period (43 per cent of the survivors) 19 returned to the same job and 11 to different lighter jobs Of the nonworking patients 26 had returned to work but stopped, most of them because of symptoms of chronic cardiac disability, average period of employment being 13 months Most of the nonworking group were unemployed because of persistent disabling cardiac symptoms

Ten patients continued work through the critical period after coronary occlusion having taken less than a week off The diagnosis for some reason was not promptly recognized Most of these did not consult a physician and continued normal activity, even though strenuous Thus in some cases if the area of infarction is small cardiac function will not be seriously impaired

the carotid sinus reflex Production of auricular fibrillation seems to be determined by the degree of vagal activity and auricular anoxemia and susceptibility of the patient Patients with congestive failure should therefore have a higher percentage of auricular fibrillation This was found to be true Congestive failure and auricular fibrillation were associated in 48 instances although it was usually impossible to determine which came first In these cases arrhythmia usually persisted without congestive failure fibrillation usually disappeared

Severe long standing cardiac damage apparently caused the persistent arrhythmia The data however, suggest that auricular fibrillation was a serious additional hazard despite presence of the previous damage increasing the death rate generally and systemic embolism specifically over that of cardiac damage alone

Rupture of the Heart in Myocardial Infarction Sidney Friedman and Paul D White[6] (Boston) report that cardiac rupture occurred in 10 of 270 instances of myocardial infarction found in nearly 3 000 autopsies at Massachusetts General Hospital from 1933 through 1940 All 10 cases of cardiac rupture (see Table p 522) were found among 105 cases of acute myocardial infarction (9 5 per cent) and none among 165 cases of old infarction

Death always occurred soon after the rupture as seen by the state of the blood in the pericardial sac and the condition of the lacerated tissue All 10 deaths occurred less than two weeks after clinical onset of acute myocardial infarction most of them within 2–10 days after the illness began

In eight cases the descending branch of the left coronary artery and the anterior wall of the left ventricle were involved In one case the circumflex branch of the left coronary artery and in one the circumflex branch of the right coronary artery was thrombosed

[See also Jetter and White following article —Ed]

(6) Ann I t M d 1 773 78 N mbe 1944

ceded or coincided with onset of myocardial infarction it disappeared in nearly three fourths of those in which it started after infarction

The patients with persistent auricular fibrillation showed evidence of pre existing cardiac damage, twice as many having history of signs and symptoms of previou cardiovascular disease as those in whom the arrhythmia disappeared One half had histories or autopsy evidence of previous infarcts and three fourths had congestive failure Nearly one third of the deaths in the group with persistent fibrillation were due to systemic emboli (arterial) as contrasted with only one ninth in the group with disappearance of arrhythmia

The effect of medication (quinidine digitalis) on auricular fibrillation was not conclusive (see Table) Quinidine

RELATION OF TYPE OF MEDICATION TO DISAPPEARANCE OR PERSISTENCE OF AURICULAR FIBRILLATION

MEDICATION	NO	DISAPPEARED NO	PERSISTED NO
None	1	5	12
Quinidine alone	11	9	2
Digitalis alone	44	6	38
Digitalis and quinidine	12	9	3
Total	84	29	55

alone was used for patients with little previous heart damage in many of whom the arrhythmia was recent and might have disappeared spontaneously digitalis alone was used for those with marked previous damage many of whom already had established arrhythmia

The question is raised as to what causes auricular fibrillation associated with myocardial infarction In experimental animals auricular anoxemia and vagal stimulation are important factors Congestive failure and auricular distention are important to the extent that they induce auricular anoxemia but neither is essential in producing auricular fibrillation Auricular fibrillation in the dog has been produced by vagal stimulation alone In coronary artery insufficiency there is hypersensitivity to vagal stimuli, as suggested by increased sensitivity of

CLINICAL DATA ON 16 CASES OF CARDIAC RUPTURE
(Jetter White p 524)

SEX	AGE	M N L DIAG	HOS 9 AY Y	DURATION O SYMP TOMS BEFO ACUTE COLLAPSE AND DE TH	HIST O HYPER NS ON	B D REST
M	72	Imbecile	0	? da (vague)	Yes	Part al
M	6	Dem praecox parano d	?1	Non	Yes	None
M	7	Alc psych chronic hallucinos s	?	11 h	Ye	Complete†
F	6	Paranoid cond t on	1	1 hr	Yes	Complete†
F	67	Dem p aecox heb type	35	None	Yes	None
M	64	Org dis CNS	1	?½ hr	Yes	None
M	64	Dem p aecox paranoid	18	None	Yes	None
F	61	Manic depressive—depressed	16	None	Yes	None
M	83	Dem praecox paranoid	38	None	No	None
F	68	Dem praecox parano d		None	Yes	None
F	63	Dem prae ox catatonic	13	None	Yes	None
F	7	Undiagnosed	0 08	None	Yes	None
M	67	Epilepsy	40	None	Yes	None
M	48	Manic depressive—manic	4	?8 hr	No	Partial
M	75	Senile psych	4?	hr	Yes	Partial
M	66	Parano a	0 5	None	Yes	None

H story lso f g p t
† Bed est d t f bepi d l h m t m

DATA ON 10 CASES OF CARDIAC RUPTURE (Friedman White, p [illegible])

Age	Sex	Duration	Sedation	Previous History	Pathologic Findings
79	M	9 da	Adequate	Angina pectoris 3 mo, hypertension	Heart enlarged, occl of d.b of L.C.A
66	M	2 da	Inadequate	None	Heart slightly enlarged occl of d.b of L.C.A. L.V infarct and laceration
80	M	7 da	Adequate but not kept in bed because of uncertain diagnosis	Slight hypertension	Heart moderately enlarged, L.V infarct and perforation occl of d.b of L.C.A
64	F	12 hr	Inadequate because of violence due to cerebral thrombosis	Angina pectoris for 5 yr, hypertension	Heart not enlarged occl d b of L.C.A., infarct of L V and R V
67	F	4 da	Inadequate because of violence due to cerebral thrombosis	Hypertension	Heart moderately enlarged, occl. of circumflex branch of R C.A infarction of posterior surface of L V with perforation
63	M	14 da.	Adequate	Angina pectoris for 1 mo	Occl of d b of L C A and circumflex branch of R C.A heart moderately enlarged, infarction of L V with perforation
51	M	14 hr	Adequate		Heart slightly enlarged occl of d b of L C.A infarct and perforation of L V
55	M	12 hr	Adequate	Angina pectoris for 2½ wk	Heart not enlarged occl of d b of L C A infarct of L V with perforation
66	F	da	Inadequate	No history	D B of L C.A occl heart not enlarged infarct of left ventricle with laceration
67	M	4 da	Adequate	Angina pectoris for 2 mo	Circumflex branch of L C A occl infarct of L V with laceration

L V —left ventricle L C A —left coronary artery d b —d[illegible]nding bra[illegible]ch
R V —right ventricle R C A —right coronary artery

most frequent initial symptoms Nontender nonpulsating enlargement of the liver with ascites and engorgement of the jugular veins are the most important physical signs The heart shadow may be small or normal but most frequently is slightly or moderately enlarged Cardiac rhythm is usually normal (13 cases) but there may be auricular fibrillation (5 cases) Abnormal cardiac sounds are usually absent but there may be slight or moderate systolic murmur Blood and pulse pressures are low or within normal limits Paradoxical pulse was present in all cases Fluoroscopic examination may show a diminution in cardiac motion and fixation of the heart in the mediastinum x rays may demonstrate a heart encased in a calcified pericardium Electrocardiograms usually are abnormal The QRS complexes showed low voltage in 17 cases and either low voltage or inversion or flattening of T waves of the coronary type The electric axis shifts only slightly with change in position axis deviation was present to the right in 6 cases to the left in 2 and normal in 10

Liver enlargement occurred in all 18 cases ascites in 15 edema of the extremities in 11 and pleural effusion in 8 Dyspnea on exertion or at rest was present in 17 and cyanosis in 14 Distention of peripheral veins and an increase in venous pressure was present in all Studies of the circulation in nine cases showed increased arteriovenous oxygen difference elevated venous pressure and prolonged circulation time diminished cardiac output per minute decreased stroke volume and lowered value for cardiac index (cardiac output in liters per square meter of body surface per minute) In seven of the nine cases these measurements of circulation were repeated after pericardiectomy with cure or improvement cardiac functional capacity increased. These tests therefore are valuable in diagnosis and estimation of improvement after operation

The 18 patients underwent 19 operations without post operative fatality Seven are classified as cured over

Rupture of the Heart in Patients in Mental Institutions Walter W Jetter and Paul D White[7] (Harvard Univ) report that in 115 consecutive autopsies on patients who died suddenly or unexpectedly in Massachusetts mental institutions 16 of 22 cases of acute myocardial infarction showed cardiac tamponade due to rupture of the heart wall at the site of the recent infarct Cardiac rupture was not found in any of the 25 cases in the same series with healed infarct only Clinical data on the 16 patients who died of cardiac rupture are shown in the table (p 523)

A definite antemortem diagnosis of myocardial infarction or cardiac rupture was not made in any case The acute myocardial infarct through which the rupture occurred was located in the left ventricle in eight instances (anterior wall five posterior wall, two, lateral wall one) involved both left ventricle and interventricular septum in seven and in one both ventricles and intervening septum were included Early fibrinous pericarditis was present in 10 and endocardial thrombosis in 9 Ruptures involved the left ventricular wall in 15 cases and the right in 1

Estimated age of the responsible infarct was two to four days in six cases two to six days in three one to two weeks in four two to three weeks in two and was not stated in the remaining case These observations strongly support the present approved therapy of bed rest during the first three weeks after onset of acute myocardial infarction

PERICARDITIS

Surgical Treatment of Chronic Constrictive Pericarditis George J Heuer and Harold J Stewart[8] (Cornell Univ) present data on 18 cases Clinical manifestations commonly are dyspnea increased size of abdomen due to hepatic enlargement and ascites, and edema of feet and ankles Dyspnea and abdominal enlargement are

(7) Ann Int Med 1 783 80 November 1944
(8) New York State J Med 45 993 938 May 1 194

may be a considerable interval between recovery from the primary acute infectious disease (often some pulmonary infection) and occurrence of symptoms of pericar

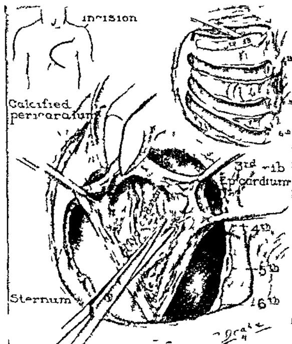


FIG 84 —Sh rp d ctı n f c t ct g p d m (p dı lysıs) and per c d m f m my d um b tte eq d f tı n f s be a f th k f l ıñ t L ft et U h p d p d l i R ght t, pp h t p dıum th gh w ll f th es t n f cart i g nd m f th d, f th fifth d th rıbs n l ft s d (t p m l h lf f ter m)

dıal ınvolvement In five cases tuberculosis was the etıologıc agent

The two conditions with which constrictive pericarditis is most likely to be confused clinically are cirrhosis and congestive heart failure due to intrinsic cardiac disease Usually, however a definite diagnosis can be made Symptoms develop slowly but are progressive Findings

periods varying from 1½ to 8½ years Six have been followed over three years and three over seven years One patient after being completely cured for 3½ years died of unrelated acute generalized peritonitis Three patients operated on more recently have shown such improvement as to warrant expectation of cure Four patients are markedly improved over periods of 3-6¼ years One died 6½ years after operation of pneumonia. One patient is moderately improved six years after operation

Four patients were not improved by operation One is living seven years after operation One patient died 1 year after operation of recurrent pulmonary infarction and two died 11 and 7 months after operation from progression of the disease To have obtained cure or marked improvement in 14 of 18 patients (77 per cent) is evidence that surgery has contributed importantly to therapy of a disease which commonly causes death

Chronic Constrictive Pericarditis Partial Pericardiectomy and Epicardiolysis in 24 Cases Stuart W Harrington[9] (Mayo Clinic) defines chronic constrictive pericarditis as an inflammatory lesion of the pericardium and epicardium in which fibrous adhesions often associated with deposits of calcium and occasionally pockets of encapsulated fluid form on and between these coverings of the heart and the inflammatory scar contracts around and onto the heart muscle so that it interferes with normal diastolic and systolic functions and causes circulatory impairment Circulatory failure develops insidiously In constrictive pericarditis, diastolic filling is less than normal and decreased stroke volume and minute output result Other factors, such as interference with systolic contraction of the ventricle may contribute to decreased ventricular output to a less but significant degree This is attributable to fixation of the scar and progressive myocardial atrophy and degeneration from limited action and the original infectious process There

(9) Ann Surg 120 468 487 October 1944

recovered are considered cured i e the patient experienced subjective relief and was able to work Actual damage to the heart undoubtedly is not entirely relieved and life expectancy is probably decreased Two patients have improved strikingly In two others recently operated on progressive improvement has occurred Two patients who recovered from the operation have shown moderate improvement and three have died since operation Two deaths were due to continuation of the disease one to progressive cardiac failure and the other to tuberculous peritonitis Another patient was improving satisfactorily but died of pneumonia seven months after operation

Of the six patients who died in the hospital success probably would not have been obtained in two with extensive tuberculosis and one with extensive myocardial degeneration and calcification of the wall of the ventricle The other three were children in poor general condition because of long duration of the disease Autopsy showed marked atrophy of the muscle

The mortality rate of 25 per cent although high is commensurate with the seriousness of the disease and would have been 100 per cent without surgical intervention Eleven patients (46 per cent) can be considered cured and two others may improve to this degree The percentage of cures can be increased greatly by earlier recognition and prompt surgical treatment

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PHYSIOLOGIC DIAGNOSIS

Anginal Syndrome

Anoxia Test in Diagnosis of Coronary Insufficiency Raymond D Pruitt Howard B Burchell and Arlie R Barnes[1] (Rochester Minn) studied 289 cases in which the anoxia test was performed according to the method of Levy In 282 cases there was some clinical evidence of angina pectoris although in most of them this diagnosis

(1) J A M A 1 8 839 845 July 1 1945

include low blood and pulse pressure, faint heart sounds tachycardia paradoxical pulse and auricular fibrillation Back pressure on the venous circulation results in high venous pressure venous dilatation, liver enlargement and transudation of fluid into body tissues particularly the abdomen pleural cavities, extremities and face

Laboratory studies reveal elevated venous pressure increased circulation time and decreased hepatic function Roentgen studies usually reveal the heart to be normal or small and occasionally slightly enlarged frequently calcareous plaques are noted in the pericardium The most diagnostic electrocardiographic pattern is one in which QRS complexes are of low voltage and T waves are negative in all standard leads If QRS voltage is low in only one lead that will usually be lead I

Since chronic constrictive pericarditis is essentially a mechanical condition interfering with cardiac function it can only be relieved by surgical removal of the fibrous encasement of the heart muscle It is important that diagnosis be made early and operative treatment instituted promptly to prevent more extensive myocardial degeneration and more destructive effects on other body tissues especially the liver The greater the myocardial atrophy and degeneration the greater the surgical hazard and less satisfactory the ultimate results

Harrington performed partial pericardiectomy and epicardiectomy with epicardiolysis (Fig 84) in 24 cases Epicardiolysis designates separation of the innermost layer of the pericardium from the heart muscle and is done in addition to resection of a portion of pericardium and epicardium The operation is performed after careful preoperative preparation under general anesthesia and the patient is placed in an oxygen tent immediately afterward Other postoperative measures are directed toward removal of body fluids and aiding function of the heart and liver

Of the 24 patients operated on 18 recovered and 6 died in the hospital after operation Nine of the 18 who

In 66 2 per cent of 71 tests in which the test was electrocardiographically positive (see Table) the only significant change consisted of a deviation usually a de pression of the RS T segment totaling 3 mm or more in leads I II III and IV F Slight increase in height or decrease in negativity of the T wave in lead IV F or IV R apparently is more frequently associated with a history suggestive of angina pectoris than is depression to the iso electric or diphasic level of a positive T wave in these same leads Significant changes occurred in lead IV R and not in lead IV F in only four tests and in lead IV F and not in IV R in only two

The anoxia test is not a laboratory short cut to diag nosis of coronary sclerosis but a means of substantiating a diagnosis of angina pectoris based on fairly convincing clinical evidence In support of this conclusion 53 2 per cent of 92 patients with a history highly suggestive of angina pectoris had an electrocardiographically positive test and of 82 patients with minimal evidence of coro nary disease only 1 had significant electrocardiographic changes during the period of oxygen want Use of the anoxia test should be restricted even among acceptable cases to instances in which there is serious disagreement regarding diagnosis and establishment of a definite diag nosis is essential Presence of coronary disease is more significant in some cases than in others For a compara tively young person whose occupation entails much phys ical exertion or nervous tension restriction of activities is a greater hardship than for an elderly person When use of the anoxia test is restricted to individuals selected according to these standards possible danger to the patient s life and expenditure of time effort and mate rials by the clinician are justified by the value of in formation that can be obtained

could not have been made on the basis of clinical evidence alone results were electrocardiographically positive in 71 cases (25 per cent)

Of 92 patients whose history suggested angina pectoris the test was electrocardiographically positive in 53 2 per cent In 19 6 per cent pain was experienced but there were no significant electrocardiographic changes Results of the test were completely negative in 23 9 per cent, and unsatisfactory in 3 3 per cent Of 108 patients with an equivocal history of angina pectoris

TYPES OF ELECTROCARDIOGRAPHIC CHANGES IN 71 TESTS

CRITERIA OF LEVY	CASES	% OF 71 TESTS
1 Sum of deviations of RS–T segment in four leads is 3 mm or more	47	60
2 Partial or complete T inversion plus deviation of RS–T segment of 1 mm or more—	2	8
3 Complete reversal of direction of T wave in lead IV F	12	16 9
1 and 3	9	1
1 2 and 3	1	1 4

N hang u rel n th foll w g mb t s of crite 1 a d nd a d 3

the test was electrocardiographically positive in 19 5 per cent In 18 5 per cent there was pain but no significant electrocardiographic change, in 50 per cent results were negative and in 12 per cent unsatisfactory Of 82 patients whose histories contained few if any suggestions of a true anginal syndrome the test was electrocardiographically positive in 1 2 per cent In 11 per cent there was pain but no electrocardiographic change in 76 8 per cent results were negative and in 11 per cent unsatisfactory

Occurrence of pain unattended by significant electrocardiographic changes during a test is unlikely to contribute significantly to solution of the diagnostic problem Twenty five of 289 tests were regarded as unsatisfactory because one or several unfavorable reactions occurred In two cases in which a brief period of cardiac arrest occurred the reaction was considered dangerous

Final diagnosis of coronary disease was made for 37 patients after several weeks observation They were studied by physical roentgen and laboratory examinations and cardiograms and observation of symptoms reactions and personal attitudes Thirty showed positive electrocardiographic response All had normal resting records except two with bundle branch block These and two with coronary occlusion whose records had returned to normal showed no changes after exercise Some patients who had had anginal pain and positive results on previous tests were able later to complete exercise without pain but still showed a positive result

As a control 77 hospitalized subjects 18–69 with no cardiovascular disease were tested all had normal exertional records and satisfactory pulse responses An additional 38 patients with anxiety neuroses and symptoms of thoracic or precordial pains were tested after detailed neuropsychiatric study In none was any abnormality found Ten patients with clinically uncomplicated hypertension were normal in this respect Four of 10 patients with neurocirculatory asthenia with rapid pulse small heart and poor pulse response showed slight changes in S T waves In one patient with a stab wound in the left ventricle and flat T waves in the resting record good amplitude developed immediately after exertion with return to normal resting record in six minutes One subject with substernal pain experienced on exertion following meals was thought to be normal examination disclosed diaphragmatic hernia with considerable interference with gastric motility

In interpretation of the tests factors other than coronary insufficiency may influence the T wave True neurocirculatory asthenia may invert the T wave in leads I and II Systemic infection and thyrotoxicosis may also confuse the problem Recent smoking may cause abnormalities in some persons Even a recent attack of anginal pain may alter the result by increasing the patient's tolerance

Simple Exertional Electrocardiography As Aid in Diagnosis of Coronary Insufficiency John B Levan[2] reports experiences in an Army general hospital Patients with coronary disease with normal electrocardiograms frequently show abnormalities during a seizure of angina pectoris The seizure can be brought on by increasing demands on the coronary circulation by exercise or by curtailing oxygen tension Tests with the patient breathing 10 per cent oxygen have been tried but require refinement of equipment and careful technic because such a critical level of oxygen tension may lead to serious complications Attention was then directed to simple exercise as an agent to increase coronary demands

Since all military personnel on full duty are expected to be equally fit for strenuous physical exertion regardless of weight height, build or age one standard was used Master steps consisting of two 9 in steps up and two down were adopted as the exercise medium Fifty ascents and descents completed in exactly three minutes were fixed as the proper amount of work No one was exercised within an hour after eating or smoking A resting record was taken in the supine position, electrodes and wires were left attached and the patient carried out the exercise or as much of it as was needed to duplicate his symptoms A record was taken rapidly after he completed his last trip and repeated three and six minutes later In some cases there was a considerable lag before an abnormal record was obtained Criteria for a positive result were (1) change from positive to iso electric or negative T waves in leads I and II or in chest leads, (2) depression of S T segment of 0 75 mm or more in any lead, with the P R segment used as the iso electric level (3) change from iso electric or flat T waves to well developed positive T waves or (4) dwarfing of the QRS amplitude

(2) War Med 7 353 359 June 1945

They may have no more than mild congestive failure or moderate coronary failure Often they are in that phase of convalescence between hospitalization and return to routine Frequently the patient at a spa has suffered mild to moderate damage from coronary thrombosis more often he has a coronary insufficiency gradually increasing through the years and returns annually for a period of self-discipline and reconditioning A smaller group has quiescent and compensated rheumatic heart disease The largest group has hypertensive disease with varying degrees of myocardial damage Patients with syphilitic heart disease do not do well nor do patients prone to frequent though often mild attacks of pulmonary edema

The general plan of therapy entails a fairly thorough organization of the patient s day and is concerned largely with rest exercise diet and development of a calm outlook on life and on the cardiovascular handicap in particular Treatment includes a mineral bath the essence of which is carbon dioxide an agent of considerable potency as a cardiac and respiratory stimulant and as a vasodilator

Rest Bed Rest and Heart Disease Samuel A Levine (Boston) states that in certain circumstances rest in bed may actually increase the work of the heart Normally rest and recumbency tend to produce a slight fall in blood pressure slowing of pulse and decrease in basal metabolic demands of the body All this would decrease the work of the heart However there are other effects that unimportant in persons with a normal heart and with many forms of heart disease may act deleteriously in some cardiac patients With peripheral edema (even though imperceptible) there is increased flow of body fluids from tissue spaces into the veins and therefore into the right side of the heart during recumbency This increases total blood volume which is usually already increased in congestive failure Bed rest has the opposite

(5) Mod Co ept C d I D 1 14 3 M h, 194

In no patient was there any untoward reaction to the exercise steps They exercised merely to a point that brought about *symptoms They were accustomed* to this exercise for stair climbing is performed by every one regardless of age or occupation hence the test caused no anxiety It has proved safe and simple Results are fully as reliable and efficient as with the 10 per cent oxygen test

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TREATMENT

The Problem of American Spas is difficult, according to Richard Kovacs[3] (New York City), because of many conflicting medical social economic and political issues Improving the medical situation is perhaps the most clearcut issue but in meeting it the advancement of balneology and creation of a simple supervising agency are not sufficient If spas are not to be left drifting along with ultimate survival of the fittest, there must be a general advisory and driving force organized by spas themselves or by a friendly outside agency Only by well guided co operation of the medical profession, the public and authorities concerned can a gradual, nationwide raising of the general status of American spas be achieved and their desirable role in the national health system be fully developed

Place of Spa Therapy in Treatment of Cardiovascular Conditions According to Carl R Comstock[4] (Saratoga Springs, N Y) the spa physician must establish a maximum of cardiac reserve and teach the patient to live within his individual capacity The home physician should forward to the spa physician a summary of case history, progress notes and essential laboratory data since the spa physician is attempting to carry *on*, perhaps in great detail and with more leisure the ideas and wishes of the home physician

Only ambulatory patients are suitable for a spa regimen

(3) J A M A 127 977 981 Apr 14 1945
(4) Ibid 128 1023 10 4 Aug 4 1945

shifted from the legs where it was harmless to the lungs where it is suffocating the patient

Although the medical profession and laboratory inves tigators have been slow in appreciating these deleterious effects of bed rest patients have always been aware of them Many have stated that they felt quite comfortable during the day while they were up but dreaded the night They were in distress only in bed some even being able to do their customary work during the day Furthermore they almost invariably insisted that when they became short of breath in bed relief was obtained by sitting straight up with their feet hanging down or by getting out of bed and walking around Although other factors may be involved the obvious inference is that posture and effect of gravity on circulation must be most impor tant in production of these distressing symptoms

Prolonged treatment in bed involves other possible hazards The most serious is phlebothrombosis and pul monary embolism particularly in cardiacs and the elderly This serious complication is more likely if the patient is immobile or debilitated if there is abdominal distention producing pressure on the pelvic veins if circulation is slow and if the patent has required seda tives

Other complications of prolonged bed rest may be hypostatic pneumonia atelectasis bed sores and rarely renal stones and bladder difficulties Men frequently re quire catheterization with its hazards of infection Some elderly individuals with prostatic hypertrophy develop urinary retention (probably avoidable if they had been allowed to stand up to urinate) Economic and psychic consequences of prolonged confinement to bed often are disastrous when they might have been avoided or miti gated by shortening the program of rest

Some of the undesirable consequences of bed rest can be avoided in treatment of heart disease When pulmo nary congestion is the main hazard the ordinary bed may be made to tilt downward from head to foot by placing

of the desired effect, as improvement usually accompanies a decrease rather than an increase in blood volume

Assumption of the horizontal position by patients with nocturnal paroxysmal dyspnea and normal individuals decreases serum concentration (dilution from increased blood volume) and slightly increases venous pressure Serum protein rises toward normal levels about 15 minutes after cessation of an attack of dyspnea These observations indicate that recumbency produces hemodilution and increased blood volume This change in dynamics of circulation may be temporary, but while it occurs it is harmful for it increases the work of the right side of the heart When the right side can respond to the increased burden it delivers more blood into the pulmonary circulation Difficulty may now arise if the left ventricle cannot expel or receive this added volume of blood per unit of time With left ventricular failure pulmonary congestion may increase because of inability of that side to keep pace with the right The same may be true with marked mitral stenosis for added blood may not be able to flow through the narrow valve and will back up into the left auricle and pulmonary vessels

These changes seldom result in appreciably harmful effects Simultaneous therapeutic measures such as digitalis and diuretics undo and mask the slight untoward influences However cardiacs often become slightly worse for a few days after being put to bed, before they begin to improve Observations on vital capacity of the lungs and velocity of blood flow before and after putting cardiacs to bed showed decrease in the former and slight slowing of the latter before real improvement began It is only when underlying treatment of the cardiac condition is not successful that one sees gross evidence of the harm done by bed rest A patient may become more and more breathless or develop definite hydrothorax not present a few days before when he was ambulatory Often the physician is erroneously optimistic because edema of the legs has disappeared when actually the fluid has

paroxysm occurred recurrently and in each of these a definite causative factor was established Results constitute evidence of the value of lanatosid C for prophylactic therapy in cases of paroxysmal auricular tachycardia and flutter

[Except for more rapid gastro-intestinal absorbability I still fe l there is no advantage in using these glucosides of digitalis rather than the whole leaf preparations However I still have an open mind on th subject as more and more art cles are being written by well trained clinicians claiming better results with the glucosides than with whole leaf preparations —Ed]

Action of a Glucoside of Digitalis (Lanatosid C) on Organically Diseased but Objectively Compensated Hearts and on Normal Hearts was evaluated by E W Erickson[7] by studying quantitative changes in cardiac function The roentgenkymogram actually serves as a cardiometer for the human heart and by the technic of Keys and Friedell one can determine volume changes and stroke output Work of the heart can then be determined by multiplying stroke output by mean blood pressure and an efficiency index can be calculated from the formula for mechanical efficiency which in the case of the heart is equivalent to dividing heart work (stroke output multiplied by mean blood pressure) by the multiple of the diastolic volume and a constant Since the constant is indeterminate it is impossible to obtain an absolute value If the same technic is used for recording tracings and computing the silhouette area results of this method of determining cardiac output and volume accurately reflect changes in these functions in the same case and relative differences in a series of cases

Thirty nine patients with compensated heart disease had normal venous pressures and arm tongue circulation time of less than 20 seconds There was no clinical evidence of congestive failure The patients were ambulatory and were seen only at the time of roentgenkymographic determinations made in duplicate before digitalization one week and three weeks after beginning digitalization and in 18 six months after cessation of

(7) P oc St ff Meet M y Cl 0 263 69 J ly 5 1945

9 in blocks under the head posts A period of rest in a chair is preferable to confinement in bed and may prove lifesaving Many patients, especially those with primary left ventricular failure, are better treated if during the first period they are allowed to sit in a chair most of the day and to walk around the room for short periods using the inclined bed at night Even when patients are kept in bed, it often is wise to permit them to go to the bath room or to use a commode When bed confinement is employed, leg exercises and other methods of preventing peripheral thrombosis should be instituted in appropriate cases

Prophylactic Use of Lanatosid C in Auricular Paroxysmal Arrhythmias is reported by Ralph M Tandowsky[6] (Los Angeles Gen l Hosp) Use of lanatosid C orally in preference to other digitalis preparations seems reasonable because this drug acts rapidly, yet with minimal toxic effect and retains its pharmacologic potency in vivo for at least 24 hours Its effect electrocardiographically and clinically has been demonstrated to be without variability whereas other preparations of digitalis act with marked inconsistency Toxic effects of this drug when administered over a prolonged period are less than those of other digitalis preparations in common use

In eight cases lanatosid C in some unknown way reduced the recurrence frequency of paroxysmal auricular tachycardia and flutter from 4 2 in a 12 month period to 0 37 in a 15 month period following use of the drug in full digitalizing dosage at onset of an initial paroxysm Amount of drug used prophylactically did not exceed 0 5 mg daily in seven cases in the eighth, dose was 1 mg Electrocardiographic evidence of effect of the drug on the RS T segment and T wave was noted Associated cardiac lesions in no way altered the result The only untoward effect was appearance from time to time of ventricular premature contractions In three instances one

(6) Am Heart J 9 71 77 J nu ry 1945

creased after digitalization This difference in trends of systolic volume in abnormal and normal hearts gives the clue as to how digitalis changes stroke output work and

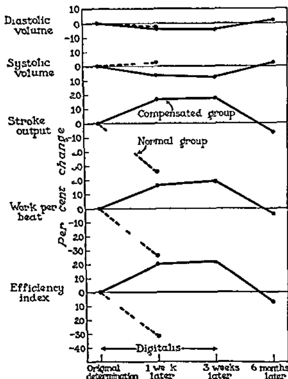


FIG 85 —D [illegible] (F m Am H rt J 29 348 M 19 194)

efficiency index in these hearts In the abnormal heart a greater proportion of total energy liberated was converted to useful work with resultant increase in force of systolic contraction or decrease in systolic volume As a result the heart empties itself more completely and

digitalization Both normal persons and patients with compensated heart disease received 6 mg lanatosid C by mouth in 48 hours and were then given an oral maintenance dose of 0 75 mg daily

Results showed that digitalis will increase mechanical efficiency of hearts of most patients with organic heart disease that are not yet clinically decompensated, whereas digitalis will decrease mechanical efficiency of a normal heart The 18 patients restudied after cessation of lanatosid C had a mean increase of 32 per cent in their efficiency index when digitalized but six months later had a mean decrease of 7 per cent from the original pre digitalis levels Fifty per cent of the patients were no better off six months after administration of digitalis was discontinued than before it was started, and 50 per cent were definitely worse

Degree of improvement in the efficiency index in abnormal hearts bore no direct relationship to heart size or type of heart disease Twelve patients with circulation times in the transition zones between 16 and 20 seconds had a mean increase in efficiency index of 40 per cent whereas 26 patients with circulation times below 16 seconds had a mean increase of 18 per cent Apparently patients with circulation times between 16 and 20 seconds are definitely closer to frank signs and symptoms of cardiac failure than those with strictly normal circulation times and a good increase in mechanical efficiency can be expected when digitalis is given patients with circulation times above 16 seconds despite absence of clinical signs of heart failure

Figure 85 illustrates mean changes produced by digitalis in various cardiac functions which determine mechanical efficiency Both normal and abnormal hearts showed a decrease in diastolic volume when digitalized i e total consumption of oxygen (energy liberated) was reduced slightly in both groups Systolic volume decreased even more in abnormal hearts than did diastolic volume whereas in normal hearts systolic volume in

(Univ of Habana) studied dogs rabbits and frogs In the frog the vagal tone is normally elevated and the heart muscle exceedingly sensitive to cholinergic drugs nevertheless digitalis produces its negative effect on cardiac chronotropism by direct action and without vagal participation i e after suppression of vagal action by atropine In the dog vagal tone is likewise elevated and the myocardium equally sensitive to vagomimetic drugs but since the conductive system is not as predominant as in the frog under the influence of digitalis the ventricular contractions become more energetic and prolonged while transmission of nervous stimuli and frequency of contractions are less affected To obtain a bradycardia equal to that in the frog one must wait some time and so that the animal does not die rapidly digitalis must be given in fractionated doses The bradycardia thus proves to be a toxic phenomenon which becomes evident prior to the terminal phase Administration of doses equivalent to therapeutic doses in man does not produce appreciable slowing of cardiac contractions Retardation of cardiac action produced by digitalis was obtained also after section of both vagal nerves indicating that it was not due to action of the drug on the cardiac inhibiting bulbar center of the vagus nerve The rabbit almost entirely lacks vagal tone and it is not easy to obtain digitalis bradycardia nevertheless bradycardia was produced after section of both vagi

It could be argued that reduction in frequency of cardiac contractions is a reflex effect caused by hypertension supposedly produced by digitalis In animals toxic doses of digitalis can produce hypertension, but in conventional clinical doses the modifications of arterial tension are merely a response to the action of digitalis on the heart muscle aimed at restoration of cardiac function impaired by the insufficiency This mechanism explains the changes in arterial tension following administration of digitalis in heart failure Therefore administration of digitalis is indicated in myocardial insufficiency whether

stroke output and work increase It follows, therefore that organically diseased hearts have already suffered a defect in energy utilization and digitalis tends to correct this defect by increasing mechanical efficiency That stroke output and work of these hearts is increased by digitalis does not indicate that they are put under greater strain As a result of increased diastolic volume these compensated hearts develop more total energy per stroke than do normal hearts and when enlarged hearts increase their mechanical efficiency they will expel much more blood per beat than will the normal heart if diastolic volume remains approximately the same Increase in systolic volume in normal hearts, on the other hand indicates that digitalis acts as a myocardial poison in this group It reduces mechanical efficiency or percentage of energy converted to useful work Consequently force of systolic contraction decreases, systolic volume increases and stroke output and heart work decrease

It may be concluded that every heart is endowed with ability to work at a given mechanical efficiency which cannot be increased by digitalis However, when organic heart disease reduces this inherent mechanical efficiency digitalis tends to restore mechanical efficiency toward normal levels Digitalis is definitely indicated for organically diseased and enlarged hearts which appear clinically compensated when circulation time is greater than 16 seconds Digitalis does no harm and is probably beneficial for many hearts when circulation time is less than 16 seconds but since the main objective in digitalizing this group is to increase life expectancy and physical fitness and to ward off clinical heart failure, long observation will be necessary to determine the ultimate benefit of digitalis

[This study is a most valuable contribution to the problem of when to digitalize a patient —Ed]

Experimental Study of Role of Vagus Nerve in Retardation of Cardiac Contractions Produced by Digitalis, and Its Clinical Interpretation Oscar Jaime[8]

(8) Rev de med y l Hab 49 480 510 O 1 31 1944

tients treated with electroshock 38 of whom had cardiovascular disease Most of the patients had mental depressions, and psychiatric results were in general good Nineteen patients had presumptive to positive evidence of coronary artery disease all these withstood electroshock with no untoward manifestations

Five patients with auricular fibrillation were treated during presence of this abnormality

Woman 51 with known rheumat c heart disease for many years had cardiac decompensation for the third time on admiss on for psychiatric treatment there were pronounced ascites and dependent edema Treatment consisted of di_gitalization acidification with potassium nitrate and repeated injections of salyrgan without improvement She then received electroshock therapy a total of 56 convuls ons in 15 months during which salyrgan was given intermittently the asc tes and edema never entirely cleared The mental condition gradually improved and it was possible to lengthen the interval between treatments A year after cessat on of electroshock treatments she was well mentally but was receiving regular salyrgan injections

Woman 40 had rheumat c heart disease and one previous episode of decompensat on Decompensat on developed after her tenth treatment which responded promptly to digitalization and administration of d uret cs, so that no further electroshock was necessary

Woman 75 had no history of cardiac disease or vascular hypertension but had gene alized arterios lero s and moderate cardiac enlargement She withstood treatment without incident

Woman 48 had had rheumatic heart d sease for several years decompensat on had not occurred. About three months following occurrence of a cerebral embolus with right hemiplegia a schi o phren c psychos s developed Three months later another embolus lodged in tl e left leg Collateral c culation was establ shed and 10 months late electroshock was inst tuted 16 treatments being given in two months There was no noteworthy change in the patient s physical cond t on but she improved mentally and six weeks after discharge was in good spirits and adjusting well to her hemiplegia

Woman 50 extremely emaciated (he _ht 61¼ in we ght 6 ½ lb), had rheumat c heart di ease but no episodes of decompensation. After four electroshock treatments she was cheerful affable and co-operative and ate her meals Two days after the last treatment she had chest pa n and scattered râles and temperature was 10_ F Temperature subsided with sulfameraz ne but chest pain continued Seven days after the last electroshock treatment dyspnea cyanosis and shock de eloped suddenly with death in an hour An electrocardiogram taken a half hour before death was not definite

or not insufficiency is associated with hypertension

Results obtained in animal experiments explain the effect of digitalis in man The condition of the myocardium is the primary factor in cardiac response to the drug In myocardial insufficiency ability of the muscular fibers to contract is impaired and systoles are weak, the contractions are not sufficient to throw a physiologic blood volume into the circulation or convey to it the normal velocity The weakened systole impedes emptying of the coronary arteries and this in turn results in insufficient nutrition of the heart muscle The muscle dilates to compensate for its diminished function and becomes more irritable and more susceptible to stimuli This physiopathologic mechanism explains the acceleration of ventricular contractions in cardiac insufficiency and their retardation by digitalis which restores full systoles and consequently coronary circulation thus rendering the myocardium less irritable

The myth of vagal participation in slowing of heart action produced by digitalis has lost all foundation Digitalis in nontoxic doses does not produce essential changes in frequency of ventricular contractions in normal subjects Moreover it exerts its optimal effect in cardiac insufficiency without tachycardia Retardation of heart action by digitalis is only a secondary phenomenon to its positive inotropic action and consequent restoration of coronary circulation and improvement of myocardial nutrition

Electroconvulsion Shock Therapy and Cardiovascular Disease Deliberate induction of convulsions in the presence of known or suspected cardiovascular disease would seem hazardous However when the convulsion is induced by application of an electric current to the brain there is no direct trauma to the cardiovascular system and one would expect no more trouble than would follow one or two minutes of strenuous exercise

Vernon L Evans[9] (Aurora, Ill) reports on 750 pa

(9) Ann Int Med 2 69 895 M y 1945

between an unpleasant diet and cardiac failure uremia encephalopathy or blindness the diet is the lesser evil Eighty three patients with acute or chronic primary kidney disease and 130 with hypertensive vascular disease with or without cardiac involvement retinopathy or uremia, were given a diet limited to rice sugar fruit and fruit juices supplemented by vitamins and iron

This diet contains in 2 000 calories about 20 Gm protein 5 Gm fat 460 Gm carbohydrate 0 2 Gm sodium and 0 15 Gm chloride Small amounts of extra sodium chloride or hydrochloric acid were given patients with hypochloremia or symptoms of salt deprivation Fluid intake was limited to about 1 000 cc fruit juices daily From 700 to 1 050 calories is provided by dry rice which contains about 350 calories per 100 Gm Additional calories are supplied by sugar and fruits No salt is permitted All juices but tomato or vegetable are allowed The rice is boiled or steamed in plain water or juices without salt milk or fat Palatability depends on cooking

Weight loss may occur in the first 20 days because (1) caloric requirements are not met by the intake in which case the quantity must be increased unless weight reduction is indicated (2) the full diet is not eaten during the first period and (3) there is loss of edema the most frequent cause Hospitalization facilitates study and treatment in the early weeks on the diet Bed rest is not indicated unless severity of the disease requires it On this management many have experienced relief from giddiness headache mental sluggishness and depression and easy fatigability However objective results such as loss of edema and changes in urine and blood chemistry blood pressure eyegrounds heart size and electrocardiograms have been used in evaluating the treatment

For some patients who had shown satisfactory improvement the diet later was modified with nonleguminous vegetables or small amounts of potatoes lean beef chicken fish or eggs (no salt or fat) usually on insistence of the patient However even these slight modifica

enough to verify a diagnosis of pulmonary embolism autopsy was not done and exact cause of death remains uncertain.

Treatment was given to nine patients with hypertension (systolic blood pressure over 200 mm Hg) In no case were complications encountered during administration of electroshock

Woman 56 had hypertension approaching the malignant phase she had had a cerebral vascular accident a few months before admission and there were a coarse tremor and slight hyperreflexia of the right arm A provisional diagnosis of psychosis due to cerebral arteriosclerosis was made Because the husband was anxious that something be done for the mental condition shock treatment was instituted After eight treatments the patient seemed hopelessly confused and unable to answer the simplest questions However within three weeks she became oriented pleasant and cheerful and was discharged cured of her mental illness Diagnosis was revised to involutional psychosis melancholy type Sixteen months after discharge her physician reported that she was well mentally, but that there was no change in the hypertension

Three other patients with previous cerebral vascular accidents were treated with electroshock with no untoward results

Woman 44 with rheumatic heart disease without decompensation had a harsh presystolic murmur, some cardiac enlargement and an inverted T wave in the fourth lead of her electrocardiogram She was given 15 electroshock treatments with no complications and no noteworthy change in her mental condition (chronic schizophrenia)

Besides the one death and development of decompensation already mentioned there was only one other complication

Woman 70 whose electrocardiogram was normal and who showed no evidence of cardiac disease other than generalized arteriosclerosis before treatments developed auricular fibrillation after 1 treatments She returned for further electro hock therapy after 11 months At that time auricular fibrillation had ceased and it did not recur with administration of 10 more treatments

[Psychiatrists have electrocardiograms of all patients before using electroconvulsion shock therapy This increases the income of the cardiographic laboratories in the various hospitals but I doubt that such study has much value to the patient or the psychiatrist A good clinical history and cardiovascular examination by a cardiologist would be of much more value —Ed]

Compensation of Renal Metabolic Dysfunction Walter Kempner[1] (Duke Univ) contends that in a choice

(1) N rth C l M J 6 61 87 Feb y 1945

between an unpleasant diet and cardiac failure uremia encephalopathy or blindness the diet is the lesser evil Eighty three patients with acute or chronic primary kidney disease and 130 with hypertensive vascular disease with or without cardiac involvement retinopathy or uremia were given a diet limited to rice sugar fruit and fruit juices supplemented by vitamins and iron

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For some patients who had shown satisfactory improvement the diet later was modified with nonleguminous vegetables or small amounts of potatoes lean beef chicken, fish or eggs (no salt or fat) usually on insistence of the patient However even these slight modifica

tions may spoil the effect In critical conditions the change may cause recurrence of signs and symptoms of the disease, hence a strict diet should be adhered to indefinitely

The diet was followed for 4 days to 32 months most patients receiving modified diets after 2–5 months It was ineffective in 75 patients (35 per cent), including 27 in a critical condition when it was started and who died 23 days later on the average The diet was beneficial to 139 patients (65 per cent) In no instance was it harmful.

With this diet protein equilibrium is maintained and urinary nitrogen excretion decreases to less than that found in fasting individuals Plasma proteins and hemoglobin remain constant Chloride concentration in plasma and urine decreases Nonprotein nitrogen determinations were made on 171 patients before and after the diet. Of 148 who survived the observation period 35 showed no decrease or an increase In 113 patients the level decreased from an average of 53 1 to 36 mg In 57 of 63 patients urea nitrogen determinations showed a decrease from 23 4 to 11 6 mg Of 82 patients with serum cholesterol determinations 73 showed a decrease from 266 to 183 mg

Of 192 patients with hypertension 25 died after 6–81 days on the strict diet There was no improvement in the hypertension in 60 of the remaining 167 patients In the other 107 patients decrease in mean arterial pressure varied from 20 to 96 5 mm. Hg Electrocardiograms of 23 of 82 patients showed a definite change in T_1 in 3 from upright to inverted and in 20 from inverted to upright Six of 76 patients showed cardiac enlargement and in 66 the heart was smaller Thirty three patients with marked vascular retinopathy were studied In 1 it became worse in 11 showed no advance or partial improvement and in 21 either improved greatly or cleared.

Oxygen Toxicity Effect of Inhalation of High Concentrations of Oxygen for 24 Hours on Normal Men at Sea Level and at Simulated Altitude of 18 000 Feet Julius H Comroe Jr Robert D Dripps Paul R Dumke and Margo Deming (Univ of Pennsylvania) report that 100 per cent oxygen administered to a large group of normal young men continuously for 24 hours produced substernal distress in 82 per cent Vital capacity was usually decreased significantly and signs of nose and throat irritation were common Control subjects breathing room air through the same apparatus did not experience these symptoms Intermittence (up to 15 minutes rest every 3 hours) did not decrease incidence of complaints Seventy five per cent oxygen produced symptoms in only 55 per cent of the subjects and 50 per cent oxygen produced no symptoms during the 24 hour period Since oxygen tents or catheters rarely produce alveolar oxygen concentrations higher than 50 per cent these forms of administering oxygen are completely safe

Breathing of 100 per cent oxygen at high altitudes (low total atmospheric pressures) does not produce symptoms indicating that symptoms are due to high oxygen tensions and not to elimination of nitrogen. Use of 100 per cent oxygen for short periods is probably safe in all patients but when oxygen must be given in excess of 12 hours concentration should be reduced to 60 per cent unless this is insufficient to saturate the arterial blood if 100 per cent oxygen must be administered careful check should be made for symptoms most likely to result from high oxygen tension

Mechanisms of Fainting According to George L Engel[3] (Univ of Cincinnati) fainting or syncope generally refers to a transient reaction terminated by brief loss of consciousness in which there is decrease in tone

(2) J A M A 128 710 717 July 7 1945
(3) J Mt S i Hosp 12 170-190 M y-J e 1945

of postural muscles and falling Since unconsciousness is usually implied, the terms syncopal reaction or fainting reaction are used when referring to the symptom complex which terminates before loss of consciousness In many types of fainting unconsciousness may be forestalled by assuming the recumbent position Patients may deny fainting because they have never lost consciousness which they prevent by lowering the head or lying down Terms used by most patients to describe syncopal experience include giddiness, light headedness dizziness graying out' blacking out spots before the eyes faintness etc In referring to these symptoms the term vertigo is incorrect

The eight major pathophysiologic disturbances related to fainting are fall in blood pressure in the erect position—vasodepressor syncope or chronic orthostatic hypotension, cardiac asystole local changes in cerebral blood flow, paroxysmal changes in cardiac rhythm obstruction of blood flow from the left ventricle anoxemia, acapnia and hysteria

Effect of Smoking Cigarets and Intravenous Administration of Nicotine on Heart and Peripheral Blood Vessels Grace M Roth John B McDonald and Charles Sheard[4] (Mayo Foundation) made 66 observations on six normal subjects all of whom were inveterate smokers and inhaled Cutaneous temperature was measured while subjects were supine wearing lightweight short pajamas When an unlighted cigaret was puffed for the period it usually took to smoke two standard cigarets there was little or no change in cutaneous temperature of extremities blood pressure or pulse rate When two corn silk cigarets were smoked cutaneous temperature decreased in only two instances 0 1–0 7 C in the toes and 0 6–2 C in the fingers, blood pressure and pulse rate were practically unchanged Smoking corn silk cigarets caused no nasopharyngeal irritation or coughing When two standard cigarets were smoked there was an average decrease

(4) M Cl N rth America 29 949 957 J ly 1945

in skin temperatures of the toes of 1 8 C (range 0 7–4 3 C) in the fingers average decrease was 3 2 C (range 1 2–6 5 C) The greatest decrease in any one digit was 4 3 C for the toes and 7 7 C for the fingers

When French ashless cigaret papers were used with the amount of tobacco in a standard cigaret or with corn silk effect on cutaneous temperatures of the extremities blood pressure and pulse rate corresponded to the effect produced by the respective cigarets alone The British filter holder with standard cigarets produced the same decrease in cutaneous temperatures of the extremities and the same increase of blood pressure and pulse rate as did standard cigarets alone

When the subject was fully clothed and in a sitting position and during slow walking with thermocouples placed inside socks and shoes decrease in cutaneous temperature of extremities was similar to that found under basal conditions

A more or less linear relationship exists between skin temperature of the toes and basal metabolic rate When two standard cigarets were smoked decrease in skin temperature depended partially on whether basal metabolic rate was low or high Individual basal metabolic rate increased with smoking of two standard cigarets and decreased with smoking of two corn silk cigarets

All electrocardiographic tracings made after smoking standard cigarets showed increased heart rate averaging 16–36 beats a minute Decreased amplitude of T waves was noted in all subjects Average decrease was 1–2 mm in all leads and in a few instances the T wave in lead III became iso electric Tracings made after smoking corn silk showed no changes in amplitude of T waves Changes in amplitude of the QRS were negligible and in no instance was there an increase in P R or QRS intervals Physiologic salt solution and nicotine were administered intravenously Basal tracings were made and an infusion of isotonic solution of sodium chloride was started when basal tracings had been made under these

circumstances without the subjects being aware of the change 2 mg nicotine was given through the same apparatus Electrocardiographic tracings made during administration of physiologic salt solution showed no increase in heart rate and in one instance showed a decrease with no change in amplitude of T wave or a maximal decrease of 0 5–1 mm After intravenous administration of nicotine tracings showed an average increase of heart rate of 30–40 beats a minute In all subjects there was an average decrease in amplitude of T waves of 1–3 mm in all leads and in a few instances the T waves demonstrated negativity in lead III Changes in amplitude of QRS were negligible and in no instance was there an increase in P R or QRS intervals

Blood pressure pulse rate and electrocardiographic tracing were normal in 5–15 minutes after smoking ceased while peripheral vascular constriction as evidenced by decrease in skin temperature, persisted 30–60 minutes There was some variation in degree of response to smoking in different subjects and in the same subject from day to day

Since vasoconstriction was not evident during puffing of an unlighted cigaret or during smoking of corn silk cigarets mechanical effort of smoking was not a factor in production of vasoconstriction Various cigaret papers also were not a factor in its production Previous observations by others were confirmed in regard to peripheral vasoconstriction as evidenced by decrease in skin temperatures and elevation of blood pressure and pulse rate produced by smoking of standard cigarets and by a similar amount of nicotine injected intravenously Electrocardiograms made after smoking standard cigarets and intravenous injection of a similar amount of nicotine were strikingly similar

Certain Unsolved Problems in Cardiology are discussed by Fredrick A Willius[5] (Mayo Clinic)

The problem of appalling increase in coronary arterial

(5) Arch. Inst de cardiol de México 14 126-134 1945

disease and its increasing appearance among younger persons resolves itself into need for determining causes of atherosclerosis and arteriosclerosis Hypotheses concerning causes of these conditions include (1) hereditary susceptibility to arterial damage (2) stresses of modern life (3) high protein diets (4) infections such as typhoid fever true influenza rheumatic fever and syphilis (5) excessive use of tobacco and (6) disturbance in lipoid metabolism No single concept fits all circumstances and etiology of atherosclerosis and arteriosclerosis and therefore of coronary disease still is unknown

Numerous unsolved problems exist regarding subacute bacterial endocarditis particularly relating to pathogenesis There is general agreement on two fundamental issues regarding its development (1) pre existence of valvular injury or congenital defect and (2) presence of transient bacteremia (usually due to Streptococcus viridans) However these fail to explain the many cases in which under apparently identical circumstances the disease does not develop State of hyperimmunity local tissue resistance and low virulence of micro organisms seem to permit focalization on the endocardium but why does it occur in some cases and not in others? Several questions arise regarding platelet thrombi (1) Do platelet thrombi develop before or because of bacteremia? (2) Is their development based on unique mechanical or immunologic factors or both? (3) What is the role of mononuclear endothelial cell proliferation? (4) Are endocardial defects a requisite for development of platelet thrombi? (5) Do bacteria always find lodgment by direct contact with the mural endocardium or does embolic valvulitis play a role in some cases? (6) Is current opinion regarding local resistance of injured valves a mere presumption?

These questions are important because treatment of subacute bacterial endocarditis is discouraging Analysis of over 3 000 reported cases revealed cures in only 2 per

cent including spontaneous recoveries but not cases of patent ductus arteriosus with superimposed bacterial endarteritis cured by surgical ligation

Etiology of chronic constrictive pericarditis associated with calcification of the pericardium is uncertain Although rheumatic fever commonly produces pericarditis and may obliterate the sac constriction rarely occurs and deposition of calcium in pericardial tissues is still more uncommon Tuberculosis explains only a few cases Occasionally a history of previous intrathoracic infection is elicited Questions regarding etiology are (1) Is the primary pericardial infection so insidious that symptoms are not apparent? (2) What factors influence great variations in course? (3) What infection accounts for most cases? (4) Does predominance of the disease among males have etiologic significance?

Paroxysmal tachycardia, particularly auricular and nodal presents numerous unsolved problems Although paroxysmal accelerations may occur with various heart diseases they are more common when the heart is not diseased The statement that the cause of accelerated heart action is a rapid succession of abnormal stimuli usually resident in an ectopic focus beyond the sinoatrial node sheds no light on the cause The condition has also been explained on the vague basis of a focus of increased cardiac irritability

For many years considerable speculation has centered on the role of the cardiac vagus and parasympathetic nerves Recently it has been shown that subcutaneous administration of acetyl beta methylcholine in certain instances causes sudden cessation of the paroxysm of tachycardia Its effect appears similar to that occurring from stimulation of the vagus and parasympathetic nerves These observations raise a question regarding possibility of periodic lowering of the normal choline content of blood and tissues occasioned perhaps by a rise in cholinesterase However these are merely speculations

Even in ventricular tachycardia in which cardiac disease is the rule or in which abnormal drug reactions have occurred exact cause of abnormal tachycardia remains obscure

Paralysis and Nervous Disorders of Cardiac Origin Ricardo Fandiño Iglesias[6] states that the best known peripheral form of paralysis of cardiac origin is that of the left recurrent nerve clinically characterized by dysphonia Paralysis is usually insidious but may be sudden and transient Bilateral paralysis of the recurrent nerve has been reported Various etiologic theories regarding this paralysis have been advanced among others compression of the nerve by the dilated left auricle and presence of mediastinitis of inflammatory syphilitic or rheumatic origin Another form of peripheral paralysis is that of the radial nerve in patients with hyposystole which recedes with improvement in clinical condition

Hemiplegias of cardiac origin include those occurring in endocarditis especially in mitral lesions those of cardiac insufficiency and of cardiac arrhythmias and the transitory paralyses in cardiac patients Hemiplegias associated with endocarditis result from embolism of branches of the left sylvian artery They may be ushered in by jacksonian convulsions or coma and may be associated with hemianesthesia and aphasia One or several episodes of hemiplegia may occur In malignant endocarditis hemiplegia often indicates the terminal phase In the Libman Osler type of endocarditis a patient who presented a febrile stage with splenomegaly and valvular involvement may develop hemiplegia with or without aphasia or fleeting episodes of hemiparesis the hemiplegia may be the first clinical manifestation of endocarditis In cardiac insufficiency hemiplegia may be one of the symptoms in a known cardiac or it may occur suddenly in a patient with latent cardiac ailment and thus represent the first episode of circulatory insufficiency

(6) P t 17 1 11 5 N 15 1944

In sinus bradycardia cerebral episodes are rare but they are relatively frequent in cardiac block. Their intensity depends on duration of cerebral ischemia. According to Vaquez a ventricular pause of 3 seconds produces simple clouding of consciousness, that of 8 seconds causes syncope and that of 15 seconds an apoplectiform or epileptiform crisis

Some patients with cardiac ailments experience transitory paresis of the face, limbs, eyes etc, lasting from a few minutes to a few hours These are apparently caused by minute emboli which without producing occlusion of the vessels cause irritation of the endothelium which in turn gives rise to muscular spasm Acetylcholine in large doses is said to give excellent results in overcoming these pareses

Heart Disease in the Jungles of the South Pacific Some Observations among Melanesians of the New Hebrides and Solomons Islands Area are reported by Albert Salisbury Hyman[7] (M C U S N R) Since many cardiovascular disturbances are said to result from modern civilization certain common forms of heart disease in a jungle background were evaluated Hyman s conclusions regarding heart disease in these natives were based on personal observations and information obtained from native practitioners and personnel of the French Colonial Service

Arteriosclerosis and vascular degenerative diseases are common inhabitants of the jungle age quickly and die in the forties and fifties Generally blood pressure level are not unlike those found in Americans or Europeans of similar age weight and sex However a small group of Melanesians was discovered with hypertension most of these were interrelated Hypertension in others apparently was due to renal damage from blackwater fever and other tropical infections Hypertensive cerebral accidents are known to the natives

Simple cardiac hypertrophy is common it was appar

(7) Ann Int Med ? 639 652 May 1945

ently unrelated to any discoverable type of heart disease Cardiac irregularities were also found Most were sinus tachycardia with high rates Extrasystolic arrhythmias were next in frequency One case of auricular fibrillation was seen, and paroxysmal tachycardia was said to occur Heart murmurs were chiefly of the functional systolic pulmonic type Apical systolic functional murmurs were next in frequency A group of aortic valvular diastolic murmurs was seen there was speculation as to whether these were due to syphilis or syphilis like tropical infections No presystolic murmurs were found rheumatic fever is rare among Melanesians as compared with the Polynesians in the South Pacific

The typical syndrome of acute coronary occlusion with pain or angina pectoris is rare conversely chronic coronary heart disease is common The latter is the cause of most cases of congestive heart failure The natives have many digitalis like jungle remedies for treatment of dropsy Absence of the pain pattern in these coronary syndromes led to experiments to determine the pain threshold of natives as compared with that of Negro personnel from a naval construction battalion unit there was no significant difference in the two groups Psychosomatic mechanisms developed by life in civilized communities may be the answer to this important question which merits investigation since it bears directly on the concept of heart pain

Peripheral vascular disease was also seen these cases were probably due to the high incidence of arteriosclerosis and atheromatosis and secondary results of jungle infestations of the feet or a combination of both Varicose veins and thrombophlebitis are common

Heart Disease in the South Autopsy observations in 1 045 cases of death due to heart disease at Charity Hospital in six years were studied by Alice Baker Holoubek[8] Causes of death and precentage of incidence were hypertensive heart disease 40 5 arteriosclerotic

(8) Am H rt J 9 168 177 F bru ry 194

heart disease 20 7, syphilitic cardiovascular disease 18 2 rheumatic heart disease 11 1 congenital heart disease, 2 2, toxic heart disease, 2 1 bacterial infection, 2 1, anemia 0 7 avitaminosis 0 5, combined 0 5, hyperthyroidism 0 4 pulmonary disease, 0 4, other types 0 3 unknown, 0 2, trauma, 0 1

The hypertensive group included over twice as many Negroes as whites, with males predominating in both races Peak number of deaths according to age begins approximately 20 years earlier in Negroes than in whites (40 compared with 60) The high incidence of hypertensive heart disease in this survey verified the similarly high clinical incidence reported from southern states where the high percentage of Negro patients is undoubtedly an important factor

There were more whites than Negroes among those who died of arteriosclerotic heart disease and males predominated in both races 59 3 per cent of this group showed evidence of myocardial infarction coronary occlusion or both Sex and race distribution in this group were practically the same as in the entire group with arteriosclerotic heart disease age distribution was substantially the same in both races Arteriosclerotic heart disease occurs with similar frequency in reports from practically every section including Mexico Hypertensive and arteriosclerotic heart disease caused death in 640 cases (61 2 per cent of the total number) including 190 cases (18 1 per cent) in which both conditions were present

The ratio of deaths due to syphilitic heart disease in Negroes and whites was roughly 6 1 with four times as many males as females Incidence was about the same as in other reports originating in the South and much higher than that reported from northern clinics as would be expected

Incidence of rheumatic heart disease was higher than that given in four of six other reports originating in southern states but much lower than that reported in northern states Chavez found an incidence of 41 per

cent in Mexico City which tends to disprove the common belief that rheumatic heart disease is rare in semi tropical and tropical regions

Gastro Intestinal Symptoms of Progressive Myocardial Disease Robt L McMillan Fred E Cowden and J B Reinhart[9] (Wake Forest College) state that presence of nausea and vomiting does not always imply primary digestive tract disease This is borne out by the fact that drugs such as digitalis may produce these symptoms by direct reflex action from the heart Disorders of the heart may produce reflex disturbances of the stomach and vice versa Nausea and vomiting are not uncommon symptoms of cardiac disease especially that resulting from inadequate coronary flow These symptoms may under certain conditions be induced reflexly from the heart itself

The authors report on a man 44 with hypertension and myocardial infarction whose predominating symptoms at onset and throughout the illness were nausea and vomiting Progressive cardiac insufficiency ensued resisting all therapy The usual causes of vomiting and nausea in congestive heart failure are drugs visceral congestion vitamin deficiency stimulation of the vomiting center by metabolites (i e uremia) and extensive myocardial damage In the case presented the authors attribute the nausea and vomiting to the last factor mentioned having ruled out the others

The mechanism of nausea and vomiting in progressive myocardial disease is thought to be analogous to the effect of digitalis which acts directly on the myocardium producing the reflex action In coronary thrombosis with pre existing sclerosis of the smaller arterial branches a vicious cycle may ensue resulting in progressive myocardial fibrosis and perpetuation of the cycle

Gastro Intestinal Conditions Simulating or Aggravating Cardiovascular Disease William Earl Clark[1]

(9) Am Hea t J 9 580 587 M y 1945
(1) J A M A 128 35 356 J 1945

(Washington, D C) states that pressure, burning or chest pain is a common symptom causing a patient to think of heart disease Substernal pain occurring especially after effort or emotional upset and lasting about 60 seconds is most likely angina However, cardiospasm or lower esophageal irritability can produce pain in the same areas as actual angina pectoris

Diaphragmatic or hiatus hernia may be confused with cardiovascular disease because of symptoms suggestive of coronary disease The situation is further confused by the fact that the conditions occur in the same age group and may occur in the same individual Gallbladder disease adds further to the problem Hiatus hernia is likely to present symptoms when the hiatus is small, because part of the stomach herniated through the diaphragm may be caught or become incarcerated

Jones in 128 cases of hiatus hernia, found that food intake especially a large meal started substernal pain in 15 of 25 cases, half being shoulder and arm pain Lying down initiated symptoms of substernal pain less frequently Glyceryl trinitrate gave some relief but not the characteristic relief seen in angina Belladonna or other antispasmodics relieved chest pressure in 17 of 18 cases Belching helped temporarily Those with small hernias had symptoms mimicking angina pectoris Exertion causes pain more consistently in coronary disease than in hiatus hernia Dietary indiscretions and nervousness most frequently precipitated chest pain

Patients with atypical cardiac respiratory or pressure symptoms under the lower sternum especially those who are older and obese should be studied for hiatus hernia Patients with hiatus hernia associate the pain with eating infrequently they may have symptoms after effort

Many nervous patients complain of chest pain at the outer border of the heart or in the chest wall it may be burning or pinching or they may have difficulty describing it Nervous or psychoneurotic patients are sub-

ject to irregularities and cardiac palpitations but a careful history and physical examination possibly with electrocardiography will usually rule out cardiovascular disease

Cardiovascular disease may be simulated or aggravated by cholecystitis or cholelithiasis A diseased gall bladder may produce the trigger mechanism initiating angina pectoris In these cases if the patient is in relatively good condition and has gallstones cholecystectomy often relieves both gallbladder disease and heart symptoms

Many executives who work hard with little recreation and rest and who are overweight and smoke excessively complain of gaseous indigestion and epigastric discomfort often referred to the chest They may be short of breath after exertion because of overweight and lack of enough exercise Most of them fail to have pressure or pain after exertion but complain of atypical sensations like dragging or pulling in the left chest which is worse under emotional strain Cutting the amount of tobacco used and reducing the schedule usually give relief Reassurance that the heart is normal emphasizing that the symptoms are due to strain and excessive use of tobacco gives a sense of security and brings mental relief

Complete Heart Block Maurice Campbell (Guy s Hosp) presents 64 cases of heart block mostly complete Age sex distribution and etiology were similar to those reported in other series There were 51 men and 13 women In lower grades of heart block the difference of sex incidence is absent or less marked Most patients were between 60 and 69 with 84 per cent over 50 The commonest cause was myocardial disease (see Table) rheumatic or syphilitic cases being excluded The latter two groups formed about 11 per cent of the total and congenital lesions 13 per cent Graybiel and White s figures are given for comparison

About half the hospital patients with complete heart

(3) Brit H rt J 6 69 92 April 1944

block have Stokes Adams attacks A patient who has not had an attack by the time he is first seen need not be alarmed about them, the chances being he will never have one and after six months of freedom their onset becomes much less likely Prognosis is then judged on the presence of congestive failure angina pectoris etc Two main forms of attacks are syncopal or epileptiform depending on duration of cardiac arrest In the syncopal form the patient feels faint and giddy, turns pale and breathes

ETIOLOGY OF COMPLETE HEART BLOCK

ETIOLOGY	NO OF CASES		AVERAGE AGE	
	Author's Series	Graybiel and White Series	Author's Series	Graybiel and White Series
Rheumatic	3	[illegible]	54	41
Syphilitic	5	3	42	43
Myocardial*	56	47	64	63
Congenital	10	4	4†	6
Diphtheritic	0	4	—	35
Combined causes	0	11	—	—
Total	74	72	—	—

* High blood pressure 10, coronary atheroma 17, cardiac failure 4 and cardiac enlargement generally with atherosclerosis but without the previous features 25

† Present age of the seven known to be alive is 30

rapidly In the epileptiform type, onset is abrupt, the person falling and often trauma results as there is loss of consciousness

Average heart rate was between 28 and 40 in most cases After gentle exercise the rate may rise only a few beats per minute however some patients may show considerable increase In 10 cases classified as hyperpietic average blood pressure was 225/108 this being high compared with that in ordinary cases of hyperpiesis In the other cases systolic pressure was above and below 160 in almost equal numbers average figures for these two groups being 194/81 and 137/73 Although the slow forceful heart beat with its long diastole has been said to produce a high systolic pressure to maintain the circulation adequately and with more ce … a fall

in diastolic pressure this does not seem to be the whole explanation as half the cases showed little increase in pulse pressure Probably a more important factor is the atherosclerosis of the aorta which is marked in many of these cases

There is a close association between bundle branch block and complete heart block Typical or atypical bundle branch block was present in nearly 30 per cent Three patients with aortic stenosis and complete heart block also had the bundle branch type Although complete *heart block may persist the rhythm changes and different* grades of block are observed The change may vary from partial block to normal rhythm with a normal P R interval However complete block may be transient or paroxysmal when it follows infarction or an acute infection or is idiopathic

Fifty cases observed for some time furnish the basis for prognosis Thirty four patients died 10 in less than a year 9 in 1–2 years 14 in 2–6 years and one after 12 years average of survival was 2½ years Of the 16 survivors 2 were observed for less than 2 years 8 for 2–6 years and 6 for 7–20 years average 6 years

Rhythmic changes did not seem to affect prognosis except when associated with Stokes Adams attacks Complete heart block with or without latent block did not affect prognosis Thirty three patients had Stokes Adams attacks Prognosis for these was much poorer than for those who did not have such attacks mortality being 80 per cent for the former as against 50 per cent for the latter Of the patients with Stokes Adams attacks 61 per cent died suddenly of those without the attacks only one is known to have died suddenly and 50 per cent died in failure

Use of Drugs in Resuscitation from Electric Shock Cecil K Drinker[3] (Harvard Univ) lists drugs shown by animal experimentation to stimulate breathing strychnine sulfate picrotoxin metrazol nikethamide

(3) J A M A 128 655 666 J 30 1945

block have Stokes Adams attacks A patient who has not had an attack by the time he is first seen need not be alarmed about them, the chances being he will never have one and after six months of freedom their onset becomes much less likely Prognosis is then judged on the presence of congestive failure angina pectoris etc Two main forms of attacks are syncopal or epileptiform depending on duration of cardiac arrest In the syncopal form the patient feels faint and giddy, turns pale and breathes

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Diphtheritic	0	4	—	55
Combined causes	0	11	—	—
Total ..	74	72	—	—

High blood pressure 10 coronary atheroma 17, cardiac failure 4 and cardiac enlargement generally with atherosclerosis but without the previous features 2

† Present age of the seven known to be alive is 80

rapidly In the epileptiform type, onset is abrupt, the person falling, and often trauma results as there is loss of consciousness

Average heart rate was between 28 and 40 in most cases After gentle exercise the rate may rise only a few beats per minute however, some patients may show considerable increase In 10 cases classified as hyperpietic average blood pressure was 225/108 this being high compared with that in ordinary cases of hyperpiesis In the other cases systolic pressure was above and below 160 in almost equal numbers average figures for these two groups being 194/81 and 137/73 Although the slow forceful heart beat with its long diastole has been said to produce a high systolic pressure to maintain the circulation adequately and with more certain some fall

tion is started heart and blood vessels will begin to show effects of oxygen lack. Oxygen will remedy this condition and no injection or treatment other than artificial respiration is required or advisable

2 The medulla in addition to the breathing center contains in very small space centers for regulating heart rate particularly for slowing the heart and for regulating blood pressure by controlling the caliber of the smallest vessels Shock which stops breathing can readily affect nearby units concerned with circulation, and consequent situations may vary breathing may be absent and the heart slow and weak with low blood pressure breathing may be present the heart slow and blood pressure variable but becoming low breathing may be irregular with a tendency to stop the heart slow irregular and weak and blood pressure low Such situations may vary among themselves so that the condition of the circulation can be appraised only by a physician capable in cardiology with at least some knowledge of the consequences of electric shock. Ordinarily patients suffering from electric shock do not receive discerning treatment

Artificial respiration for absent or inadequate breathing is essential If breathing is feeble and unreliable oxygen carbon dioxide inhalation is helpful Absolute rest is imperative If blood pressure continues to remain low and the heart feeble so that there is danger of circulatory inadequacy intravenous injection of a small dose of epinephrine or ephedrine may be considered Injection should be given slowly and should be understood to be a last resort Caffeine and sodium benzoate given early will benefit circulation

3 The shock by passing through the heart may cause ventricular fibrillation The patient is dead white bluish No pulse can be felt and after three breaths respiration ceases Such patients are o
injections of epinephrine through the chest wall
into the heart There is increasing evidence tha
ular fibrillation occurring spontaneously in m

(coramine), caffeine and sodium benzoate, and alpha lobeline In nonpoisonous dosage, strychnine has no appreciable effect on breathing and when given in sufficient amount to stimulate breathing momentarily, it is eventually depressing to respiration and aggravates the condition When enough picrotoxin is injected to stimulate breathing convulsions result Metrazol is a strong stimulant of the nervous system but has no conspicuous effect on breathing and no value in respiratory failure from electric shock. Although nikethamide has some promise as a stimulant of a depressed breathing center its value is uncertain and is not worth serious consideration in electric shock therapy Caffeine has a general stimulating effect on the central nervous system, including the breathing center There is no evidence that it does harm, hence an intravenous injection of caffeine and sodium benzoate is not out of place in respiratory depression, but injection must be made directly into the blood by vein, since prompt action is imperative Alpha lobeline has been abandoned owing to its capricious effect as a stimulant to breathing and its disadvantageous effects on the heart and circulation

There is no substance which can be given by injection which benefits breathing significantly Caffeine and sodium benzoate intravenously may be useful but has no specific potency However since prolonged artificial respiration through prevention of asphyxia, sometimes results in recovery more than this could be done in the direction of finding some direct aid to the respiratory center, and in such a direction will come the greatest advances in resuscitation of the most serious electric accidents

The following circulatory derangements may be met in electric shock (1) The shock by passing through the medulla may have stopped breathing, and left circulation of the blood somewhat impaired but not seriously This is the ideal case for resuscitation But if breathing is absent for four or five minutes before art[illegible]l respira

The patient with a cirsoid aneurysm marked edema and dilatation of the leg vessels showed a 25 1 per cent increase in total blood volume A patient with an arterio venous aneurysm of the superficial femoral vessels and extensive edema of the extremity enormous venous dilatation and a sanguineous pelvic tumor had a 49 3 per cent increase in blood volume In a similar case but more advanced there was 75 1 per cent increase in blood volume The three patients with increased blood volume were those who had increased minute cardiac volume

Of three patients studied during manual compression of the femoral artery two exhibited bradycardia Minute volume was the same as before compression while venous pressure rose in all three

Venous Thrombosis and Pulmonary Embolism Review of 202 Patients Treated by Femoral Vein Interruption is reported by Robert P Linton[5] (Massachusetts Gen'l Hosp) Both unilateral and bilateral operations were done with a total of 280 deep veins interrupted Eighty one per cent of the patients were over 40 Leg signs or symptoms were the first indication of venous thrombosis in 59 per cent while chest pain appeared first in 41 per cent A few minor infarcts after femoral vein interruption occurred in 11 patients Massive fatal pulmonary embolism did not follow bilateral femoral vein interruption Treatment of minor pulmonary infarction following femoral vein interruption is administration of heparin or dicumarol There were 12 deaths in this series Fatal pulmonary embolism occurred in only one instance in which the embolus arose from the uninterrupted vein in the opposite leg No deaths were directly attributable to the operation Proximal thrombi were safely aspirated in 86 cases During operation the patient's trunk is elevated to insure a positive venous pressure at the groin so that thrombi will be forced distalward rather than be aspirated toward the heart

Persistent edema is the commonest sequela following

( ) C cti t M J 9 255 262 April 1945

usually fatal occasionally ceases with return of the heart to normal rhythmic beating There is no reason to believe the same thing may not happen after electric shock, but such an event must be rare

There is no practical procedure which affects the fibrillating heart muscle and intracardiac injection of epinephrine can be relied on to do but one thing, namely make fibrillation worse so that any chance of spontaneous shift to normal pulsation is lost

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THE PERIPHERAL BLOOD VESSELS

Respiratory and Circulatory Changes in Arteriovenous Aneurysms Alberto C Taquini and Jorge R F Suarez[4] studied five patients with arteriovenous communications four males with traumatic fistulas (three of the superficial and one of the deep femoral vessels) and one woman with cirsoid aneurysm of the leg Pulmonary ventilation was increased in all averaging 4 4 L per sq M as against 3 65 L normal average Actual increase was probably greater for three patients had marked edema and thus increased body surface area Carbon dioxide concentration in expired air was diminished respiratory quotient and tension of carbon dioxide in the alveolar air was within normal limits as were vital capacity and residual air

Minute cardiac volume was frankly increased in three patients, evidently the result of altered circulatory dynamics arteriovenous oxygen difference was definitely below normal in two of these and within the lower limits of normal in one Venous pressure investigated in three patients was normal Total blood volume was increased in three cases, plasma cell ratio was normal in all five Blood volume showed a certain relation with the clinical picture One patient with an arteriovenous aneurysm of the deep femoral vessels of four months duration but without other symptoms had normal total blood volume

(4) Medicl Méxic 5 109 119 J nuary 1945

Present Trends in Treatment of Varicose Veins are reviewed Kenneth Wade Thompson[6] (Tufts College Med School) states that since patients requiring treat ment cannot wait for solution of all the problems regard ing varicose veins he has adopted a general treatment policy Injection procedure alone is reserved solely for obliteration of small subcuticular spidery bursts or other small superficial varices treated for cosmetic rea sons Conceivably injections might also be used for pal liative treatment of a chronic varicose ulcer in a patient who cannot take time to submit to the complete surgical procedure When there are no demonstrable incompetent communicating veins and no contraindications for sur gery all varicose veins are treated by high ligation and division of the saphenous vein with retrograde injection A more radical procedure based on Sherman s sugges tions is applied to those with obvious incompetent com municating veins below the saphenofemoral junction

To avoid pulmonary embolism at least two precautions are necessary (1) The saphenous vein is ligated exactly at the saphenofemoral junction (2) Patients with simple ligation are activated almost immediately and those with the more extensive procedure are encouraged to move about the bed and to be out of bed most of the time fol lowing operation this is done at expense of optimal treat ment of the wounds

Surgical treatment of varicose veins in the presence of activity of the phlebitic syndrome should not be lightly undertaken

Phlebothrombosis of Femoral and Iliac Veins Fred eric W Bancroft[7] (Columbia Univ) reviews 13 cases in which thrombectomy was done the clot in the femoral vein extended upward beyond Poupart s ligament into the iliac vein often as far as the bifurcation of the vena cava In nine cases antecedent emboli were present

In three cases bilateral thrombectomy was done the

(6) C t M J 9 62 69 Ap 7 1945
(7) S Cl N rth Am rica 25 3 5 33 April, 1945

femoral vein interruption, but is no greater than if the phlebitis is allowed to run its course Postoperative edema diminishes more rapidly after aspiration of the thrombus than with conservative treatment Immediate edema following operation is more frequent after common femoral interruption than after superficial femoral vein interruption After a year there seems little difference in amount of edema Although incidence of edema a year after operation was 45 per cent, swelling was minimal and practically all patients had discarded any form of supporting bandage or stocking Only one transient post phlebitic ulcer was observed It is hoped that femoral vein interruption may prevent postphlebitic varicose ulcerations

It is believed that deaths from pulmonary embolism have been prevented by femoral vein interruption and that morbidity of thrombophlebitis of the lower extremities has been greatly reduced Average hospital stay after ligation was 8 4 days, the shortest 3 days and the longest 13 days

This operation should be carried out on patients with nonfatal pulmonary embolism even though no positive signs of venous thrombosis in the legs can be detected and on any patient with deep phlebitis of the lower extremities All signs of phlebitis are seldom present, so decision to operate may depend on one or two criteria Bilateral femoral vein interruption should be done on all patients even if the diagnosis is made only in one extremity because frequently a thrombus is found in the unsuspected femoral vein Diagnosis of thrombophlebitis should be made, if possible before femoral and iliac veins have become involved, since postoperative sequelae are reduced Interruption of the inferior vena cava distal to the renal veins is the operation of choice in cases of long standing thrombophlebitis with pulmonary embolism No serious sequelae resulted in 10 inferior vena cava interruptions Eight patients are living and well, and the two deaths were not attributable to the ligation

of a young woman who first observed color changes of the type of Raynaud s phenomenon on exposure to cold In the early stage only the tips of the fingers of both hands are involved Later modifications in color may involve the hands Color changes may consist solely of cyanosis or pallor but more commonly there are three phases pallor, cyanosis and rubor Symptoms are worse in cold and better in warm weather Pain is not prominent during the attack or in the interval between attacks Paresthesia however is common during the attack and consists of numbness, tingling burning a feeling of tightness or a pins and needles or sticking sensation in the fingers During the attack the fingers are cold and in many instances there is actual diminution of sensory acuity Slight swelling of involved fingers may occur and may persist even between attacks

In progressive or advanced stages Raynaud s phenomenon may become disabling in severity and frequency Attacks may occur on exposure to a slightly cool environment and under almost any emotional stress so that even warmer weather may afford little relief Sclerodermatous changes often affect the skin of the involved parts and result in considerable interference with normal use particularly of the fingers Although extensive gangrene does not occur gangrenous ulcerations on tips of the digits may persist and cause considerable discomfort Occasionally these lesions become infected and necessitate amputation of the distal parts of involved fingers

Identification of Raynaud s disease is relatively easy when Raynaud s phenomenon occurs without evidence of a secondary cause and when it is bilateral It should have existed long enough for any secondary cause to have become evident before final diagnosis is made Criteria for diagnosis are (1) episodes of Raynaud s phenomenon excited by cold or emotion (2) bilaterality of the phenomenon (3) absence of gangrene or limitation to minimal grades of cutaneous gangrene (4) absence of any other primary disease which might be causal such as

operations being performed simultaneously by two surgical teams One patient (Case 2) had a thrombectomy on the left side followed about two weeks later by thrombectomy on the right

CASE 2 —Embolism occurred after cesarean section, but there was no evidence of femoral thrombosis until 10 days A clot was removed from the left femoral vein but it was felt that the upper end of the clot had not been reached since free bleeding did not occur Infarct occurred in the right lung eight days later eight days after that phlebothrombosis developed in the right thigh and a clot was removed from the femoral vein. She began to go into collapse during administration of anesthesia this state continued after thrombectomy until death three days later It was believed that emboli were showered from the pelvic veins although examination of the uterus showed no evidence of broad ligament involvement

There was one other death in this series, in a case of bilateral extensive carcinoma of the ovaries Thrombectomy was performed simultaneously with removal of the tumor and the patient died two weeks later of renal insufficiency with no evidence of return of thrombosis

One patient continued to have persistent swelling of the thigh and leg after operation In the others the leg returned to normal size fairly rapidly and there have been no complaints of interference with function

In Case 1 it was possible to inspect the vein two weeks after thrombectomy

Woman 46 had a tender uterine fibroma in the lower portion of the pelvis, for which hysterectomy had been recommended While awaiting operation acute phlebothrombosis occurred in the left iliac and femoral veins there was no evidence of pulmonary embolism However since hysterectomy was necessary soon because of the degenerating fibroid it was thought advisable to remove the clot from the iliac vein beforehand This was done and she was treated postoperatively by subcutaneous injections of heparin. Two weeks later while she was still under heparinization a supracervical hysterectomy was performed Palpation of the iliac vein revealed no evidence of clot in the lumen There were however some old thrombi in the veins of the broad ligament Convalescence was uneventful

Diagnosis of Raynaud s Disease According to Edgar A Hines Jr[8] (Mayo Clinic) the typical history is that

(8) M Cl North Am ica 29 94 949 July 1945

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occlusive arterial disease cervical rib or organic disease of the nervous system, and (5) history of symptoms for two years or longer The most important point is elimination of any possible secondary factor secondary Raynaud's phenomenon is much more common than Raynaud's disease

In differential diagnosis inquiry should be made as to contact with heavy metals and ergot Family history of similar disturbances may be helpful When Raynaud's phenomenon has been restricted to one finger or one extremity for a long period, some secondary causative factor should be suspected When Raynaud's phenomenon occurs in a man thrombo-angiitis obliterans or some other organic factor should be suspected In differential diagnosis the prime object is to rule out occlusive arterial disease

Thrombo angiitis obliterans is most commonly confused with Raynaud's disease for three reasons emphasis which Raynaud gave to symmetric gangrene resulted in confusion, Raynaud's phenomenon often occurs in both upper and lower extremities in early stages of thrombo angiitis obliterans and symptoms of Raynaud's disease and of thrombo angiitis obliterans usually begin in early adult life Difference in sex incidence alone should indicate the diagnosis in most cases since Raynaud's disease occurs largely among females and thrombo angiitis largely among males In thrombo-angiitis obliterans one extremity is usually involved first, in Raynaud's disease both upper extremities are usually involved first When Raynaud's phenomenon is present with thrombo angiitis obliterans it is likely to involve only one or two digits even in late stages A history of recurring superficial phlebitis should also suggest thrombo angiitis obliterans final diagnosis of which can be made by demonstration of permanent arterial occlusion

Other conditions that might, in rare instances be confused with Raynaud's disease are arteriosclerosis oblit

erans acrocyanosis livedo reticularis chronic pernio and acroscleroderma

Anatomic Lesions in Peripheral Vasospastic Disease Domingo Mosto and Antonio T Schena[9] (Buenos Aires) performed biopsies on digital arteries in seven patients with Raynaud s syndrome and found progres sive anatomic changes varying according to intensity of the clinical syndrome With vasospastic symptoms they found thickening of the intima and with more advanced changes a more marked hyperplasia of the intima hyal ine and fibrous degeneration and finally marked con striction of the lumen Inflammatory changes in the form of intense perivasculitis were present only in cases which progressed to gangrene requiring amputation of the toes These inflammatory changes the authors consider to be secondary to the gangrenous process and preceding abscesses Study of amputated toes revealed extension of the degenerative vascular changes to the various arterial branches and smallest arterioles of the skin

The cutaneous glomus regulates heat loss in the parts exposed to cold In peripheral vascular diseases when the canals of Souquet Hoyer are destroyed or collapsed new ones form at the expense of the preglomus arterioles. In arteriosclerotic gangrene changes in the glomus re sult from hyaline degeneration of the afferent artery In diabetic gangrene the intima of the Souquet Hoyer canal and of preglomus arterioles presents degenerative changes whereas the afferent artery remains intact In thrombo angiitis obliterans the gangrenous lesions were attributed by Popoff to abnormal arteriovenous anastomoses In one of the authors cases of Raynaud s syn drome the marked hyperplasia of the glomus system might have been implicated in the production of periph eral vascular spasms

It is difficult to establish the chronologic relationship between anatomic lesions and clinical symptoms The former may have preceded the functional phenomena or

(9) Arch Soc. argc t d anat n rm. y pat. 5 105 117 1943.

may have been secondary to continued persisting spasms on the blood vessel walls A corollary postmortem study of digital arteries in cases without history of peripheral vascular spasm revealed moderate intimal hyperplasia only in presence of an otherwise diseased vascular system, as in nephro arteriosclerosis In all other cases digital arteries were normal Therefore it seems probable that vasoconstricting nervous impulses acting on diseased vessel walls finally affect the normal threshold of vascular narrowing

Thrombo Angiitis Obliterans According to Hugh Montgomery[1] (M C USNR) peripheral arteries and veins are most commonly involved but any artery or vein may be Early arterial changes are lymphocytic infiltration of adventitia and intimal thickening resulting from cellular proliferation Thrombosis and eventually fibrosis within adventitia and perivascular tissue ensue The process is inflammatory rather than retrogressive as in arteriosclerosis Thrombosis is a necessary sequel widespread scar tissue formation, rather than calcification, is the end result

Vascular inflammation and reaction of the vessel wall produce local pain and tenderness and if a superficial vessel is affected cause localized redness These frequently overlooked manifestations are insignificant compared with ischemia caused by arterial occlusion or abnormal vasoconstriction Early vasoconstriction causes most of the ischemia Abnormal vasoconstriction varies constantly, especially with environmental temperature and is usually accompanied by abnormal cold sweating suggesting neurologic origin

Proof of abnormal vasoconstriction can be established by relief of cutaneous peripheral ischemic signs and symptoms after application of heat or of other methods of decreasing vasomotor tone Vasodilatation tests furnish exact information concerning the role of arterial occlusion and abnormal vasoconstriction in causing

(1) Mod. Concepts Cardiovascular Dis vol 13 no 9 September 1944

ischemia Conspicuously ischemic tissue has insufficient arterial blood supply to meet metabolic needs chronic ulceration and gangrene result

In early stages there may be tender areas of migratory phlebitis undue coldness of toes and fingers blanching or cyanosis of digits numbness and pain One or more pulses of ankles and wrists disappear With development of collateral circulation remissions may occur which last for a year or more but relapses are common during colder months Late in the disease or because of unusual trauma to feet or fingers development of indolent lesions sometimes occurs

Diagnosis is not difficult if several typical symptoms or signs occur in a young male Absence of one or more peripheral pulses and coldness of a painful extremity are highly suggestive Migratory phlebitis if present confirms diagnosis Raynaud s disease and arteriosclerosis must be differentiated

Treatment consists of measures to increase peripheral blood flow and to decrease needs for peripheral blood flow The latter means avoidance of even the most minor trauma in ischemic tissue because mixed organisms at the site of injury produce indolent ulceration Measures to increase peripheral blood flow are of two types those which produce vasodilatation and those which do not Heat drugs and all methods of interrupting vasomotor innervation are of the former type Alcohol is the most effective drug in producing vasodilatation if it is not tolerated mecholyl bromide or papaverine hydrochloride may cause slight dilatation Typhoid H antigen intravenously is useful in maintaining fairly prolonged vasodilatation Sympathectomy is usually advisable when one or at most two extremities are severely ischemic and there is no or only distal gangrene Use of measures to produce vasodilatation presupposes persistence of some capacity for dilating When this is absent Buerger s postural exercises or suction pressure therapy increases blood flow through relatively rigid arteries by rhythmi

cally increasing intra arterial pressure or decreasing pressure in ischemic tissue

Therapy must be guided by success of trials of various measures, preferably with capacity for blood flow measured by vasodilatation tests Prolonged courses of intensive therapy should be avoided when they are not clearly necessary but bed care drainage of infection suction pressure therapy nerve crushing to control pain and sympathectomy may be required when there is no improvement Extension of gangrene into the foot may be followed by demarcation which permits plastic repair thus amputation is usually avoided

Diagnosis of Thrombo Angiitis Obliterans and Peripheral Arteriosclerosis Paul S Lowenstein (St Louis Univ) believes diagnosis of thrombo angiitis obliterans depends more on careful examination by a physician conscious of the frequency of peripheral vascular diseases than on use of elaborate instrumental methods History is important and recital of excessive weakness in an extremity pain on exertion relieved by rest and reappearing on further effort should direct suspicion to the peripheral circulation Presence of these symptoms coldness and pallor of the limb or thrombophlebitis unexplainable on another basis is extremely suggestive, particularly in a young man possibly of Jewish descent who consumes tobacco in excessive amounts To prevent serious and lasting damage the disease must be recognized early

Extremities should be viewed in good light to detect variations from normal color edema or other swelling or trophic changes Red tender linear markings along the course of inflamed superficial veins or more localized cutaneous nodes are significant Temperature of the affected limb should be compared with that of the other extremity Any difference or presence of zones of sudden change suggests circulatory involvement A common finding is drop in temperature of the part which in case of sudden arterial occlusion may be strikingly cold

(2) J Missouri M A 4 77 280 May 1945

These temperature changes may be registered with the skin thermometer or electric thermocouple but for practical purposes the hand of the examiner can detect any significant variation At least four arterial pulsations should be sought—femoral popliteal dorsalis pedis and posterior tibial or axillary brachial radial and ulnar

DIFFERENTIAL DIAGNOSIS

	THROMBO-ANGIITIS OBLITERANS	ARTERIOSCLEROSIS
Age	Chiefly 30–50 av 42	Chiefly after midlife
Sex	Males about 98 per cent	Males predominate may be either sex
Race	Jews about 28 per cent	Any
Rest pain	Often severe	Usually mild
Intermittent claudication	Usually present	Usually present
General appearance	Often younger than age	Often older than ag
Upper extremities	Frequently involved	Seldom involved
Postural changes	Rubor when dependent pallor on elevation	Rubor when dependent less common pallor on elevation
Edema	Frequent	Uncommon
Arteries	Pulseless or of diminished volume coronary sclerosis rare	Pulseless or of diminished volume coronary scleros s frequent
Veins	Frequently involved often migrating phlebitis	Rarely involved
Roentgenograms of vessels	Usually negative aorta normal	Frequently calcification of vessels possibly elongation of aorta

With the oscillometer a graphic and objective picture may be obtained Effects of posture on appearance of the extremity presence or absence of pallor on elevation and degree and angle of blanching require careful study Rubor or cyanosis in the dependent position is characteristic of Buerger's disease although it is also present in other vascular diseases

In diagnosis of arteriosclerosis history is also important Symptoms merely indicate necessity for careful study of peripheral circulation and often do not vary

greatly from those of thrombo angiitis obliterans (see Table) Common early symptoms in arteriosclerosis are vague disturbances of sensation in feet and toes, frequently followed by subjective coldness Leg fatigue and intermittent claudication are common, pain at rest is less common than claudication and usually occurs later

Examination of extremities, even in early arteriosclerosis usually reveals diminished angle of circulatory efficiency as manifested by pallor of the plantar aspect of toes and feet on elevation of the leg This is more valuable than presence or absence of pedal pulses in estimating vascular status Rubor of toes and feet in the dependent position may be found in advanced stages though much less frequently than in thrombo angiitis Temperature changes do not necessarily correspond with those complained of by the patient and there may be marked changes of which the patient is unaware With more advanced circulatory involvement cyanosis may be observed, the more extensive its area, the more ominous the prognosis particularly when other signs of ischemia are present Edema is not common, unless of renal or cardiac origin Trophic changes are encountered frequently increasing in severity as circulatory condition grows worse

Wheal Fluorescence New Method of Evaluating Peripheral Vascular Diseases James Locke Neller and Erwin R Schmidt[3] (Madison Wis) present a preliminary report of a simple test which consists of observing presence or absence of fluorescence in surface scratches after intravenous injection of fluorescein followed by inspection under specially filtered ultraviolet light

Experiments with the technic recommended by Lange and Boyd in peripheral vascular disease were disappointing and the method was about to be discarded when it was discovered that use of skin fluorescence as a measure of fundamental skin response to injury resulted in a simple practical and effective test During routine

(3) A o Surg 1 1 328 33 M h 1945

fluorescence examination of a severely impaired leg it was noted that minute areas of trauma made immediately before injection of the fluorescein appeared brilliantly fluorescent from thigh to upper calf and were completely nonfluorescent below general skin fluorescence was present to the tips of the toes and absent only where actual gangrene was present Careful investigation showed that scratch fluorescence appeared only when a wheal response occurred the test therefore offers a simple way of determining ability of tissues to produce minute grossly invisible wheals to mild painless surface scratches Since wheal formation depends entirely on active vascular flow the test establishes the point distal to which vascular flow falls below a critical level Absence of fluorescence reveals an incomplete repair response and consequently must indicate delayed ability to heal This fact is further substantiated by observation of the scratch marks under ordinary light five to seven days after the test marks where fluorescence was present are practically healed but where it was absent they are still in the process of healing

The authors use a 20 per cent solution of sodium fluorescein in distilled water autoclaved in 50–100 cc colored dispensing bottles for 15 minutes and given in 5 cc doses The dye is rapidly excreted by the kidneys and other secretory glands in unchanged form It produces an icteric tint to the skin for two or three days colors urine and body secretions for three or four days and causes false positive urine sugar tests for four or five days Fluorescein probably should not be given in presence of severe kidney damage with significant nitrogen retention Fluids should be forced for two or three days after injection No serious complications have been reported although slight nausea may develop during injection

Light with a wavelength of 3 600–3 800 A reveals optimal luminescence of fluorescein An ultraviolet source may be made to transmit waves of this frequency

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(3) A n S g 1 1 3 8 337 M h 1915

point a graded degree of vascular disease exists immediate prognosis under local and general treatment is good but ultimate prognosis is guarded Amputation in areas where scratch fluorescence is absent is likely to be followed by poor or absent healing necessitating reamputation at a higher level Amputation in areas of decreased fluorescence is hazardous

Pecent Advances in Treatment of Peripheral Vascular Diseases Gordon E Jones[4] (Seattle Wash.) states that chemical agents are of little value except in treatment of certain acute episodes such as arterial embolism or thrombosis There is fairly general agreement concerning ill effects of tobacco smoke on obliterative peripheral vascular disease especially of vasospastic type Treatment of dermatophytosis is especially important in care of vascular problems not only in prophylaxis of infection but also because research has suggested the possibility of sensitization to fungus antigens in patients with thrombo angiitis obliterans and postphlebitic ulcers

Successful efforts to increase peripheral blood flow by physical measures have been limited to intermittent venous occlusion with Buerger s passive vascular exercises a Burdick intermittent venous occlusion apparatus or an ordinary blood pressure cuff

Sympathectomy improves peripheral circulation by increasing blood flow by eliminating vascular spasm increasing warmth by eliminating sweating and associated heat loss from evaporation and relieving pain In Raynaud s disease sympathetic denervation interrupts vasomotor impulses the primary initiating factor in arteriolar spasm Selected cases of obstructive vascular disease due to peripheral arteriosclerosis are benefited by sympathetic denervation Such symptoms as resting pain and intermittent claudication can be relieved or cured by this procedure in relatively young arteriosclerotics who although lacking palpable pulsations have a fair collateral circulation as evidenced by oscillometric readings skin

(4) W st. J S g 52 494 506 D mber 1944

by addition of a purple filter (Corning glass no 587-Lange) or Wood s filter

TECHNIC —In a room which can be darkened, the legs are exposed from low thigh to toes and the inner or outer aspect of each entire leg and foot is prepared by washing with alcohol Superficial scratches are made at 2 in intervals down the legs in comparable places by stroking the skin in the same spot 5–10 times with a hypodermic needle The scratches need not be deep and need not draw blood As soon as the marks are completed 5 cc of 20 per cent *sodium fluorescein solution is injected intravenously at normal* rate The room is darkened and the filtered ultraviolet light is immediately played on the scratched area The test can be read in 1-minutes it does not change appreciably and remains readable for over 60 minutes The major fact to observe is the level at which the marks cease to be fluorescent this change if present is always abrupt Another type of level marked by a definite decrease in intensity of scratch fluorescence is sometimes seen this, which may occur alone or with a lower level where fluorescence disappears should also be noted. General luminescence of the skin of varying intensity can be seen in the background but never interferes with reading of the scratch test since fluorescence in the scratched areas is much more intense and localized

Correlation with clinical examination other known tests and end results leads to certain tentative conclusions When scratch fluorescence is present to a certain level and absent beyond that point severe organic vascular impairment exists below the last fluorescent mark sufficient to affect seriously the tissue s ability to repair itself Though local and general treatment without amputation may be attended by healing the result is likely to be only temporary When scratch fluorescence is equally brilliant in all marks there is no significant organic vascular disease in the tested areas Vasospastic disease apparently does not affect the test and may be predominantly responsible for symptoms in these cases If gangrene is present distal to the last fluorescent mark at the base of the toes the process is largely local local and general treatment with removal of necrotic areas is likely to be followed by healing and return to good function When scratch fluorescence is present *throughout* but definitely decreased in intensity below a certain

Three forms of therapy are available for treatment of thrombotic phenomena novocain injections of lumbar sympathetic ganglions anticoagulants and interruption of deep venous channels between the femoral vein and the inferior vena cava

Thrombophlebitis in a patient under 40 should be treated by injection of novocain in the lumbar sympathetic ganglions supplemented with the usual conservative measures such as compression and elevation of the involved extremity In a patient over 50 both of the femoral veins should be ligated Any patient who has had a pulmonary infarct faces a mortality rate of 20 per cent from a subsequent embolus and should be given the benefit of bilateral femoral vein ligation When origin of the thrombus is definitely known and the patient is not bedridden unilateral ligation is sufficient Signs of phlebothrombosis in a patient over 40 indicate bilateral femoral vein ligation Anticoagulants are not recommended routinely and should be reserved for selected cases A passive fatalistic attitude toward phlebitis and pulmonary embolism is not justified most fatal pulmonary emboli are preventable

Ligation of Femoral Vein for Chronic Occlusive Arterial Disease S Thomas Glasser[5] (New York Med College) reviews 118 ligations in 110 patients

According to Macleod hydrostatic pressure in capillaries is 32 mm at the arterial end and 12 mm at the venular end However in chronic occlusive arterial disease capillary pressure is decreased to almost hydrostatic value Starting at the heart the force (pressure) of flow diminishes as the smaller vessels are approached so that in the capillaries the flow is fairly constant under normal conditions regardless of the intermittent changes of pressure which correspond to the cardiac systole and diastole It would be fair to assume that with an increase in venous pressure caused by ligation of a major vein the tension on the arterial side would increase sufficiently

(5) A h S g 50 566 J ry 194

temperatures and lack of marked color changes on elevation and dependency In thrombo angiitis obliterans, sympathectomy can be expected to render immediate relief in proportion to the degree that vasospasm is responsible for the clinical picture In addition to immediate relief there is prolonged benefit derived from opening and developing a collateral network of vessels

Refrigeration anesthesia is a valuable adjunct in certain types of cases Cooling arrests metabolism of both tissue and bacteria and can therefore be used to "freeze' a septic or gangrenous process while an extremely ill patient can be prepared for surgery Since refrigeration anesthesia must necessarily be associated with use of a tourniquet the method is not applicable except when it has definitely been decided to sacrifice the limb

Incidence of successful results in arterial surgery has been increased by heparin and sympathectomy Heparin acts to make earlier embolectomies successful rather than to prolong the period during which operation can be safely performed Embolectomy should be performed in the first 12 hours and surgery should be supplemented with heparin and sympathetic block Sympathectomy is recommended by some as an important concomitant measure in surgical treatment of aneurysms and arterio venous fistulas to increase collateral circulation It should be performed immediately following traumatic lesions of blood vessels in old injuries it should be performed before the surgery on the vascular lesion Immediate anticoagulant therapy is indicated as a supplement to any vascular surgery which entails blood vessel suture

Thrombosis is commoner than supposed and may be expected to occur in 27–60 per cent of hospital patients The process can be proved to originate in leg veins 45–95 per cent of the time with actual incidence probably closer to the latter figure The process in the legs is bilateral in 50–60 per cent of the cases Bed rest and varicose veins increase the incidence of these complications

nite value in prevention of gangrene and alleviation of pain Increased collateral circulation was evidenced by increased bleeding which was noted at amputation and by arteriography In six patients pulses became palpable postoperatively Pulmonary embolism was absent following amputation in these cases Ligation distal to entrance of the profunda vein probably accounts for absence of edema Thrombosis was never noted in the femoral vein proximal to the site of ligation because presence of large tributaries in this region with a swift stream of venous blood obviates this complication Final follow up examinations of 29 patients who were found alive (38 6 per cent) showed that 17 required amputation In this group 14 had been originally hospitalized with gangrene or ulcers on the toes of the 12 who remained alive and well 8 had been hospitalized with these same lesions Active lesions on the toes had been present in 88 of the 110 patients on admission demonstrating that the greatest number of patients were treated after the phase in which femoral vein ligation might be considered prophylactic However 25 4 per cent of the entire series were alive at the time of final follow up It might be reasonable to expect that had ligation been performed as a prophylactic measure only the statistical figures would have been more impressive Since no morbidity or mortality is associated with the operation it should be used more commonly in selected cases

Traumatic Neurocirculatory Disorders of the Extremities J Dewey Bisgard[6] (Omaha) states that symptoms due to neurovascular lesions of the extremities too often are attributed to neuroses and malingering actually differential diagnosis often is difficult or impossible The underlying vasomotor disturbance manifests itself variously In one group symptoms are predominantly those resulting from angiospasm in another those resulting from vasodilatation and in many cases both types exist simultaneously or intermittently Im

(6) Am J S g 47 210 16 F b ry 1945

to open up collateral vessels and augment the vascular bed in general This presupposes presence of functioning and available collateral vessels for this purpose In addition ligation of the femoral vein reduces to some degree any element of vasospasm which may be present, since some interruption in the sympathetic pathway is incidental to the procedure

Glasser s technic consists of interruption of the superficial femoral vein immediately distal to its junction with the vena profunda The 10 cm incision is placed over the course of the femoral artery starting at Poupart's ligament Transfixion of the cut ends of the vein is a safeguard against slipping of the ligature

The condition in all 110 patients was complicated by systemic degenerative disease Lesions on feet or toes such as ulcer gangrene or cellulitis were present in 88 (80 per cent) Principal diagnoses were arteriosclerosis complicated by diabetes (60 cases), arteriosclerosis obliterans (44 cases) and thrombo angiitis obliterans (6 cases) There were 43 women and 67 men, 33 women and 27 men were diabetic The largest number of patients were in the sixth decade—the youngest was 33 and the oldest 92 *Numerous less serious operative procedures* and 30 amputations on the thigh were performed 1–220 days after ligation of the femoral vein 10 patients had previously undergone amputation on the thigh Pain on admission was a prominent symptom in 61 patients, 50 were relieved following ligation Twenty patients died in hospital of intercurrent disease, in no instance was death associated with ligation

Ligation of the femoral vein is valuable in selected cases To determine indications for the procedure and a proper selection of cases ligation was performed on all patients with chronic obstructive arterial disease who consented to the operation Hence the series included patients whose condition was unfavorable or 'hopeless in view of such complications as spreading gangrene and sepsis However ligation of the femoral vein was of defi

of minor causalgias resulting from lesser injuries such as contusions sprains fractures lacerations and puncture wounds inflicted by animals Thrombophlebitis especially the inflammatory type not infrequently gives rise to the syndrome of causalgia

Both major and minor causalgias are associated with rapid demineralization of bones in the affected foot or hand These bone and joint changes are the principal source of prolonged disability and are a source of distress long after the superficial tissues have regained normal appearance Sudeck s bone atrophy not infrequently is seen with fractures about the wrist joint and may even follow relatively trivial and minor injuries

Disturbances in cutaneous sensation vary from extreme hyperesthesia to complete anesthesia and frequently paresthesia There is also deep tenderness

Treatment of post traumatic neurovascular lesions varies with the case Acute vascular contractures with impending gangrene demand immediate efforts to relieve vascular spasm by injection of regional sympathetic ganglions or periarterial sympathectomy Before treatment is undertaken in chronic cases careful neurologic and psychiatric study should be made to exclude compensation neuroses and hysteria All doubtful cases should be considered true causalgia and treated accordingly until a diagnostic therapeutic trial has proved them otherwise Major causalgias associated with injury to major nerves may be relieved by such procedures as neurolyses when the nerve is imbedded in scar excision of neuromas when present repair of a nerve when partially severed and by excision of foreign bodies in close proximity to these nerves Minor causalgias and particularly Sudeck s bone atrophy following injuries may be prevented by early institution of physical therapy When there is no definite evidence of involvement of nerves or demonstrable trigger points or when direct attack has failed sympathetic innervation of the extremity should be interrupted first by injection of anesthetic

mediately following most major injuries and often following minor ones varying degrees of pallor coldness and numbness develop in the injured extremity This condition stupeur arterielle follows woundless traumatism as well as penetrating or lacerated wounds and has been attributed to injury to the adventitia of the arteries A simple contusion of the arm can make the hand and forearm so limp and colorless and the radial pulse so nearly imperceptible that a crushing injury to the brachial artery may be suspected There are recorded instances in which these vascular contractures have been so intense and prolonged that gangrene of fingers or toes has resulted Fortunately however these phenomena are usually of short duration they have been considered comparable to surgical shock limited to an extremity During the last war there were many unnecessary amputations for stupeur arterielle If there is not an early spontaneous release of vasospasm and recovery procaine injection of the regional sympathetic ganglions should be done Application of heat to one of these ischemic extremities is a dangerous practice it merely increases metabolic demands on an inadequate circulation thereby increasing the likelihood of gangrene

Recovery from the acute state may be incomplete with development of chronic neurocirculatory conditions which result in certain trophic changes and contractures with and without pain and are similar or identical with a group of manifestations considered under the inclusive term causalgia This is characterized by *burning pain* varying from the most trivial burning to a state of torture Trigger points are often demonstrable The skin may show trophic changes the bones show much atrophy and joints are swollen stiff and painful Muscles are atrophic and are or appear to be partially paralyzed This condition is frequently related to wounds of the median and sciatic nerves and to injuries of the brachial plexus In addition to major causalgias incited by injury to large nerves and vessels there are groups

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solutions (repeated if necessary), then if this fails either *by periarterial sympathectomy or by cervicodorsal* or lumbar sympathectomy Because patients with more severe disorders are likely to become addicted to morphine every effort should be made to obtain early relief *of pain*

Surgical Management of Vascular Trauma H L Pugh[7] (M C U S N) reports on 30 cases of arterial and arteriovenous injury with particular *reference* to traumatic or false arteriovenous aneurysms The latter usu*ally result from direct injury such as a bullet, shell* fragment or stab wound A carotid cavernous sinus fistula may be caused indirectly by a fractured skull If a bullet or piercing instrument passes between an artery or vein lying close to each other, a nick in each vessel may result in immediate shunting of arterial blood into the vein, with little extraneous hemorrhage and hematoma formation Usually however there is spilling of a variable amount of blood with consequent hemat*oma which may be well delineated by surrounding* structures extend along fascial planes or dissect into soft tissues until it attains considerable size When the spread is ultimately arrested a process of absorption and organization ensues and with laying *down* of fibroblasts and connective tissue a retaining wall or sac is formed In time this sac becomes lined with the same type of endothelium as constitutes the intima of the artery and its structure acquires a tough elastic quality This sac can assume various shapes depending on resistance of surrounding structures and nature of the break of vascular walls It may be single and symmetrical or asymmetrical and multilocular or there may be two more or less separate sacs one communicating directly with the artery and *the* other *with the* vein *Numerous collateral* vessels usually communicate with the sac

Symptomatology varies with location and size of the lesion and concomitant nerve involvement Tingling or

(7) Am J Surg 68 520 Ap 1 1945

burning pain extending along the affected extremity numbness and coldness are the common subjective symptoms Locally three classic signs are pathognomonic of an arteriovenous aneurysm pulsating tumor thrill and bruit, all reaching their crescendo during systole They may all be reduced or be made to disappear entirely by pressure on the tumor or proximal to it position may also change their intensity Pressure over or proximal to the tumor will produce a slowing of the pulse (Branham s sign) Systemic changes include (1) accelerated heart rate (2) elevated systolic pressure and lowered diastolic pressure with increased pulse pressure (3) increased cardiac output and decreased stroke output (4) engorgement of pulmonary vessels (5) increased venous pressure and circulation time (6) increased circulating blood volume(?) (7) cardiac dilatation or hypertrophy and (8) electrocardiographic changes indicating cardiac damage Semilocal changes include establishment of collateral circulation dilatation of the artery distal to the fistula thinning and dilatation of the proximal artery and increase in size and length of the extremity The latter factors are not constant and depend on duration and size of the fistula Other variable manifestations are venous stasis increasing varicosities trophic changes associated nerve paralysis and limitation of joint motion

There is much difference of opinion about treatment Certain general principles may appreciably affect the situation either directly or indirectly These include (1) treatment of shock in the acute stage after injury (2) keeping the patient warm to encourage vasodilatation (3) moderate elevation of the extremity (4) interruption of spasm by interruption of the sympathetic nervous system by procaine injection or section (5) avoidance of wet dressings to keep the dry gangrene resulting from interruption of the arterial circulation dry (6) care of the local wound and (7) use of the most meticulous aseptic surgical technic

While a few arteriovenous fistulas and traumatic arterial aneurysms may disappear spontaneously, the great majority will not and such conservative treatment is not likely to be compatible with the exigencies of military service However, too early surgical intervention is definitely dangerous a minimum of two or preferably three months must elapse to allow development of collateral circulation This requires less time in young, vigorous men than in older individuals

Quadruple ligation with excision of the fistula was done in 20 cases of arteriovenous aneurysm paravertebral injection of lumbar or cervical sympathetics was used in 19 cases Gangrene developed in one case despite all efforts to prevent it, and amputation of the leg above the knee was necessary The arteriovenous fistula in this case had been present 2½ years In one case of popliteal arteriovenous aneurysm in which the artery alone was ligated, threatened gangrene was averted by prompt ligation of the vein which was followed by immediate improvement of the circulation In one patient whose axillary and axillary circumflex arteries had been severed by metal fragments ligation of arteries alone was promptly followed by dry gangrene which later necessitated amputation of the arm above the elbow This case is not included among the 20 of arteriovenous aneurysm, since only the large arteries were involved It is believed this arm might have been saved if the axillary vein had been ligated concurrently

Recovery from such disability as could be ascribed to the arteriovenous aneurysm was complete in every case All patients returned to full or limited duty unless prevented by a separate and distinct additional encumbrance

Pugh believes that quadruple ligation and excision of the involved segment is the best treatment for arteriovenous aneurysms or fistulas however it must be recognized that gangrene with subsequent loss of a limb may supervene

Two fatalities occurred in this series of cases of arterial accidents and arteriovenous trauma the first in an elderly patient who died of pulmonary embolus after embolectomy had been successfully performed on the first portion of his axillary artery the second in an elderly patient in whom a rupture in a femoral artery developed with consequent large hematoma formation In the latter case death occurred shortly after ligation of the femoral artery proximal to the rupture

Secondary hemorrhage occurred only once after one week in a patient in whom early operative intervention was regarded as imperative (due to pain and steady increase in size of hematoma) despite the known existence of infection and much soft tissue damage and necrosis After secondary ligation with the wound left open the patient went on to recovery and has a good leg

Progress in Vascular Surgery is reviewed by C B Olim[8] Injury to a major vessel often produces severe vasospasm which is usually confined to a limited portion of the vessel in the immediate vicinity of the wound but may at times involve the entire vessel This vasospasm may be much more crippling and serious than the original injury and if allowed to persist may produce gangrene of the extremity by constricting the collateral tree

Vasospasm may be controlled by use of such drugs as papaverine or by interrupting sympathetic pathways either by periarterial sympathectomy or procaine block of regional sympathetic ganglions

An important artery which is lacerated should be sutured whenever possible followed by heparinization Treatment of arterial embolism has improved since discovery of heparin which has extended the time in which embolectomy may be attempted True aneurysms may be excised or the artery divided proximally and distally and the aneurysm left in place The corresponding vein should also be ligated when there is impaired ar

(8) M mph M J 0 18 1 F ry 1945

terial flow Arteriovenous fistulas are more successfully managed in most cases by quadruple ligation of the artery and vein with excision of the mass It is important to distinguish between a true aneurysm and a fistula, for gangrene may result if the artery alone is ligated in an arteriovenous fistula Procaine sympathetic block or ganglionectomy is a useful preoperative measure when inadequate circulation exists

Prophylaxis against thrombophlebitis should be stressed in patients confined to bed with simple daily exercises of the legs and elevation of the legs at intervals In treatment of thrombophlebitis, blocking of sympathetic ganglions with procaine relieves vasospasm and facilitates venous drainage Heparin administration is also useful in preventing extension of thrombi In more severe cases, ligation of the deep vein is the procedure of choice

Nodular Vascular Diseases of the Legs Hamilton Montgomery, Paul A O Leary and Nelson W Barker[9] (Mayo Clinic) believe nodular vasculitis erythema induratum, erythrocyanosis, pernio erythema nodosum panniculitis, recurrent idiopathic thrombophlebitis, indurated cellulitis and ulceration secondary to chronic venous stasis have much in common They involve the legs primarily, they are characterized by presence of nodules and, at times ulceration, and are associated with varying degrees of blood vessel involvement and fibrosis

Differential diagnosis is often difficult clinically because of the many common clinical features Histopathologic studies of the nodules and ulcers are complicated by the etiologic relationship of tuberculosis in some of them This problem would be obviated if the sections studied all showed typical tubercle formation and Mycobacterium tuberculosis was demonstrated by section or animal inoculation

A study of clinical and histologic and other laboratory data was done on a series of 175 cases of nodular and

(9) J A M A 128 335 340 June 2 194

ulcerative lesions of the legs and 40 cases of recurrent idiopathic thrombophlebitis Patients were all white adults In almost all cases complete physical examination of the thorax was done including roentgen examination to find evidence of tuberculosis Tuberculin tests were used frequently and animal inoculation was done in recently observed cases especially when erythema in duratum was suspected.

The nodose lesions of nodular vasculitis found chiefly on the calves of women 30–40 years old are painful They are rare in men and younger women and tend to clear up with bed rest and elevation of the legs Recur rence is common but ulceration is rare some patients have a history of previous phlebitis Distribution of the lesions is the same as in erythema induratum but they are more painful and usually of shorter duration. The nodules show vasculitis with thickening and obliterative changes in the arteries and veins fibrosis of the sub-cutaneous tissue collections of foreign body giant cells and atrophy of the fat but no definite tubercle formation

The term erythema induratum is used to designate a tuberculous process either ulcerative or nodose in form. It is described as beginning with involvement of the calves of adolescent girls but it may occur in boys and men and may start at any age It may be associated with other forms of hematogenous tuberculosis and is classified under tuberculosis cutis indurativa which includes papulonecrotic tuberculids Seventy two cases in the series of 175 were classified as erythema induratum Age of onset varied from early teens to 65 years Of 11 cases in men 2 were of the ulcerative type occurring on the leg Five patients had nodose lesions and in four cutaneous tuberculosis including papulonecrotic tuberculids and scrofuloderma was present elsewhere Two of the women had lesions on their legs arms and breast In several the nodules and ulcers recurred in winter and disappeared in summer A few patients had unilateral

involvement In 21 of 25 cases, the tuberculin test (PPD) was positive with a weak first dilution Mycobacterium tuberculosis was found in only two specimens of skin Histopathologic changes are not always classic Non specific granuloma with varying degrees of vasculitis was found in more than 30 per cent More than one specimen may be necessary for diagnosis with many sections including subcutaneous tissue often being required before typical tubercles are seen There was some involvement of the arteries and veins in all the cases Periarteritis endarteritis panarteritis and phlebitis of the same types are seen involving the arterioles venules and occasionally larger vessels in the subcutaneous tissue Vascular changes may predominate to the exclusion of tubercle formation as a result of fat necrosis or marked fibrosis due to vasculitis

Telford is quoted as defining erythrocyanosis as a reddish blue discoloration of the skin seen on the lower half of the legs of girls and young women associated with indurative nodules which may break down to small ulcers and regress with residual scarring Most of the women are stout and have a florid appearance and large legs The pathology is described as obliterative vascular changes with thickening of the arterial coats foreign body giant cells fat necrosis and formation of fibroblasts and granulation tissue Both erythrocyanosis and pernio recur in winter and disappear in summer the ulcers being more superficial and the inflammatory reaction being less in pernio than in erythema induratum

Erythema nodosum is an acute disease associated with fever, malaise and arthralgia and characterized by superficial tender nodules and plaques usually on the legs The lesions last days to several weeks on resolution they leave a residual discoloration but no ulceration Attacks tend to occur in spring and autumn and are associated with streptococcic infections A chronic lesion like erythema nodosum may occur with syphilis and coccidioidal granuloma, or it may be due to use of drugs

such as bromides and sulfonamides There is infiltration about the vascular network in the upper and middle cutis consisting of lymphocytes and polymorphonuclear leukocytes The vessel walls are edematous with occasional inflammatory hemorrhagic infiltration of the walls A relatively acute infiltration with fat atrophy and necrosis in the subcutaneous tissue may occur secondary thrombophlebitis may supervene The chronic forms of erythema nodosum which have been associated with tuberculosis are examples of nonulcerative types of erythema induratum or types of nodular vasculitis

Relapsing febrile nodular nonsuppurative panniculitis is frequently associated with episodes of fever Large subcutaneous plaques and nodules predominate on the trunk and thighs instead of on the legs with subsequent atrophy and depression of the skin at the site of involution This uncommon condition occurs chiefly in women There is edema and necrosis of the subcutaneous fat with phagocytosis of the fat by different cell types a few multinucleated cells are seen with an inflammatory reaction of lymphocytes and polymorphonuclear leukocytes There is usually little fibroplastic proliferation or vasculitis There does not seem to be a definite relationship between this disease and tuberculosis

Recurrent idiopathic thrombophlebitis occurs chiefly in men and is primarily a disease of small and medium sized veins in many cases identical with the vein involvement seen in thrombo angiitis obliterans There are many discrete tender nodules on the legs and elsewhere persisting 7–18 days occurring in crops and tending to extend by segments to the larger veins The lesions are more linear than circular and are usually smaller than those of erythema nodosum and erythema induratum The symptoms are mild without necrosis and ulceration

There is inflammation of the vein wall with occlusion of the lumen by cellular thrombosis accompanied by fibrosis of the wall with little if any inflammation of adjacent tissue The veins affected are usually larger

than those involved in nodular vasculitis, erythema induratum erythema nodosum or panniculitis The small amount of periphlebitic reaction and absence of fat necrosis and fibrosis serve to differentiate it from thrombophlebitis secondary to other conditions

Chronic venous stasis following iliofemoral thrombophlebitis or long standing varicose veins may produce a subacute or chronic inflammation in the lower third of the leg with subsequent formation of a tender painful plaquelike induration of the skin and subcutaneous tissue The circumference of the leg may be involved giving the appearance of a constriction above which is pitting edema The most common site is just proximal to the internal malleolus Ulceration and secondary infection may occur with much induration of the ulcer margin

DISEASES *of the* DIGESTIVE SYSTEM *and* METABOLISM

GEORGE B EUSTERMAN M D

PART V

DISEASES OF THE DIGESTIVE SYSTEM AND METABOLISM

DISEASES OF THE ESOPHAGUS AND STOMACH

Gastro Intestinal Hormones Their Physiology and Application A C Ivy (Northwestern Univ) points out that physiologic methods and other confirmative evidence have established the existence of the hormones secretin cholecystokinin and enterogastrone Secretin has been crystallized and its crystallization confirmed It is useful for absolute diagnosis of pancreatic achylia or degeneration of pancreatic acinar tissue Cholecystokinin may be useful as a test of functional capacity of the gallbladder to empty and for diagnosis of biliary dyskinesia Enterogastrone may prove useful for management of peptic ulcer as results of animal experiments are quite convincing

Existence of the following hormones has apparently been established by physiologic methods but adequate confirmation is lacking gastrin enterocrinin and pancreozymin Gastrin may or may not be histamine Other hormones namely villikinin and enterocin require further analytic study and confirmation as to their existence as specific substances Villikinin supposedly stimulates specifically the movements of the villi and enterocin the motility of the intestine Duodenin incretin excretin and insulotrophic hormone are synonymous terms used to designate a hormone produced by the intestinal mucosa which lowers the blood sugar by influencing carbohydrate metabolism or by increasing the output of insulin Evidence of the existence of such a substance is not convincing

( ) T & St d Coll l l y a s Ph'l d lph 1 101 107 December 1944

Perforated Ulcer of Esophagus Following a Burn L M Rankin[1] (Delaware County Hosp, Upper Darby, Pa) reports a case

Boy 4 was admitted with second degree burns of the thighs buttocks and lower abdomen. Two days before he sat down in a basin of hot water The burns were treated with tannic acid jelly



FIG 86—Lower end of ophagus and tomach showi g perfo ation of lcer f soph gus.

Two days later he was not acutely ill but had a slight fever The burned areas were in good condition Prognosis seemed good Some hours later he cried out as if from a sudden acute pain and a codeine injection was necessary The general condition grew rapidly

(1) Am J Su g 67 134 1 6 J ry 1945

worse despite all efforts and he died that same afternoon. Autopsy revealed a Curling ulcer of the esophagus with hemorrhage

Since Curling first described the relation between ulcer of the duodenum and a burn many theories have been advanced as to etiology but none is entirely satisfactory and the process and relationship are unknown

Synergistic Effect of Caffeine on Histamine in Relation to Gastric Secretion J A Roth and A C Ivy[3] (Northwestern Univ) use the term synergism to characterize the response obtained when the combined action of two drugs given simultaneously is greater than that

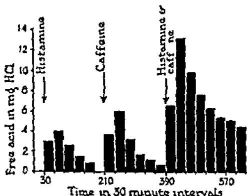


FIG. 67 —Aver ge t tal utp t f f ee a d in e ght c t ft h st m n dihyd chloride (subcuta eously) ff w th d um b ate (nt a ven u ly) a d ft both d ug multa ou ly Re po to h st mi plus aff ine is g te th n s m f ind vid al r pon nd iso prol nged

anticipated from the sum of their individual actions Cats and human subjects were used in the experiments

Results show that the gastric secretory response to histamine or alcohol is greatly increased and prolonged after administration of caffeine in comparison with the output of hydrochloric acid or gastric juice provoked by these substances before administration of caffeine Gastric secretory response to histamine or alcohol and caffeine given simultaneously is considerably greater

(3) Am J Physiol 142 107 113 August 1944

than the sum of the preceding individual responses to the same doses of histamine or alcohol and caffeine given separately an example of which is shown in Figure 87 The response to the combined action of the drugs is prolonged and maintained at a high level This type of secretory curve was obtained in each case Average per cent increase calculated on the basis of individual increments was 117 per cent

[From a practical clinical standpoint it would be interesting to study the synergistic effect of caffeine on alcohol and nicotine in cats and humans —Ed.]

Simple Procedure for Determining Approximate Concentration of Pepsin in Gastric Contents Israel S Kleiner[4] (New York City) proposes a simplification of the method described by Barowsky Tauber and Kleiner using the basic principle of the milk clotting action of

INTERPRETATION OF RESULTS

CLOTTING TIME (MIN)	TENTATIVE COMPARISON WITH NORMAL	APPROXIMATE NO UNITS/CC GASTRIC JUICE	SUGGESTED METHOD OF REPORTING
Less than 3	Very high	Over 2 500	++++
3– 4	Moderately high	. 001–2 500	+++
4–10	Usual normal	1 001–2 000	++
10–15	Low	501–1 000	+
Over 15	None to trace	0–500	0 or trace

gastric fluid at pH 5 0 Since there is no rennin in human adult gastric juice a measure of the milk clotting power is a measure of peptic activity

The length of time required for clotting in the modified method varies inversely with the amount of pepsin present as shown in the table

PROCEDURE —The buffer solution is made by dissolving 42 Gm sodium hydroxide in 500 cc distilled water 115 cc of 80 per cent acetic acid is added and the whole is diluted to 1,000 cc. Equal parts of fresh cow s milk and buffer solution are mixed well and 10 cc is used for each test Gastric contents are centrifuged or filtered if necessary, and the reaction is tested with congo red paper If acid 1 cc is diluted to 50 cc with water and mixed well If not acid a small quantity is diluted accurately with an equal volume of 0 1

(4) J Lab & Clin Med 30 634 635 J 1 1945

normal hydrochloric aci l and mixed well and 1 cc of this mixture is diluted to 25 cc with water and mixed again. One cc of the diluted gastric fluid is added to a test tube containing 10 cc buffered milk in a water bath at 30 C and mixed well the tube being quickly replaced The interval between the time when the tube is replaced and the time when the milk clots i e when it thickens on tilting the tube or small white particles separate out is the clotting time

Psychosomatic Disorders of the Gastro Intestinal Tract Edward Weiss[5] states that such disturbances occur in healthy persons subjected to unusual emotional stress and are common manifestations of emotional stress in neurotic persons Psychosomatic technics of diagnosis and treatment are therefore important in general medi cal practice Weiss cites a number of cases indicating that psychosomatic disturbances can cause various vague gastro intestinal symptoms In such cases psychosomatic diagnosis and psychotherapy are needed for successful results The gastro intestinal symptoms include consti pation with headache symptoms appearing during the male climacteric anxiety states with gastro intestinal phenomena especially a cancerphobia so called colitis cardiospasm and hypoglycemia

So far as gastro intestinal problems are concerned the psychosomatic approach permits the physician to realize that the abdomen is the sounding board of the emotion from a dynamic standpoint he will learn that bed and board are as definitely linked in the emotional life of the adult as are sustenance and sensuality in the life of the infant and from a genetic standpoint he will discover that the real social disease is in the atmosphere of the home where the foundation is laid for many gastro intestinal ills

Heartburn consists of a burning occasionally painful or rending distress beginning usually under the lower end of the sternum and sometimes extending as far as the pharynx Walter C Alvarez[6] (Mayo Clinic) reports results of questioning 123 persons with this symptom

(5) J Mt S H p 1 7 0 76 M y J 1945
(6) G t t l gy 3 1 12 July 1944

than the sum of the preceding individual responses to the same doses of histamine or alcohol and caffeine given separately an example of which is shown in Figure 61 The response to the combined action of the drugs is prolonged and maintained at a high level This type of secretory curve was obtained in each case Average per cent increase calculated on the basis of individual increments was 117 per cent

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(4) J Lab & Clin Med 30 634 635 July 1945

normal hydrochloric acid and mixed well and 1 cc of this mixture is diluted to 5 cc with water and mixed again One cc of the diluted gastric fluid is added to a test tube containing 10 cc buffered milk in a water bath at 20 C and mixed well the tube being quickly replaced. The interval between the time when the tube is replaced and the time when the milk clots i e when it thickens on tilting the tube or small white particles separate out is the clotting time

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(5) J Mt Si H sp 12 750 76 May J 1945
(6) G str t l gy 3 1 1 J ly 1944

Heartburn tends to occur in spells, an hour or two after eating, sometimes patients are wakened at night by the distress Some of the women had their worst heartburn during pregnancies, and some had it only at those times when the currents in the digestive tract tended to be reversed some women had severe heartburn in one pregnancy and not in another Few patients had any sign of organic disease in the digestive tract Seventeen patients had or had had ulcer but stated that the heartburn disappeared when the ulcer was active and reappeared when it seemed to be healed At least 26 per cent of the patients were Jewish as compared with 12 per cent in a control group suggesting a predilection for this race Heredity appears to be a factor sometimes Of the total group, 73 per cent were men suggesting some hereditary or organic cause for the trouble as nearly all organic diseases of the digestive tract except cholecystitis affect men more often than women Regurgitation and belching were common these were occasionally associated with the heartburn apparently only when the esophageal mucosa had been sensitized When the esophagus was normal regurgitation of acid gastric contents did not cause burning

Immediate causes of heartburn included eating too fast or too much certain foods such as chocolate cucumbers cream fats onions coffee, seasonings radishes tomatoes oranges eggs peppers and cabbage, some drugs such as aspirin and morphine, alcohol, tobacco emotion constipation lying down, bending over or exercising and gastric hyperacidity

Relief was obtained by a large number of patients on taking sodium bicarbonate In such cases relief is due partly to neutralization of acid in the esophagus and stomach and partly to cessation of waves of reverse peristalsis Many patients needed large quantities of sodium bicarbonate dissolved in water Some were relieved by sipping water

Analysis of the results indicates that heartburn is due

largely to regurgitation into a sensitized esophagus and partly to reverse waves of peristalsis

Stomach and Erythropoiesis Ernst Wollheim[7] (Univ of Lund) reports animal experiments which indicate a functional relationship between the stomach and erythro poiesis Such a relationship is especially clear when one considers the frequency of occurrence of achylia with hypochromic and hyperchromic anemias and of appear ance of anemias after gastric resection. The functional relations seem explicable on the basis of a metabolic sub strate for the small group of hypochromic anemias with achylia caused by lack of iron as well as for the hyper chromic macrocytic pernicious anemia caused by lack of Castle s intrinsic factor Other hyperchromic anemias such as those found with sprue and pellagra can be produced by lack of an extrinsic factor or vitamin B Such lack of extrinsic or intrinsic factor and sometimes possibly a disturbance in resorption causes a deficiency of the antianemic reaction product of the two factors which is identical with the antipernicious protective substance of the liver

Experiments were performed on rabbits and dogs causing an artificial thrombosis which in turn produced a partial or total venous block in the stomach Results indicate that the stomach produces the Castle enzyme in the pyloric glands and the antianemic addisin and also another quite different factor in the fundus This fac tor seems necessary for maintenance of normal erythro poiesis It exhibits its erythropoietic effect only when reaching the liver via the blood stream It thus requires for full effect some reaction in the liver or a liver factor This liver factor and the erythropoietic reaction prod ucts are not identical with the antipernicious protective substance of the liver

Passage of Miller Abbott Tube through Pylorus with Aid of Electromagnet Henry Mayer Jr[8] makes the

(7) S hwei m d. W hn h 73 33 238 F b 20 1945
(8) U S N M B ll. 43 463-466 September 1944

tip of the tube of a highly magnetic material alnico which is relatively noncorrosive

TECHNIC —The metallic tip is fixed on the end of an ordinary *Miller Abbott tube* this is used in conjunction with a good hand type of electromagnet With heavy patients where the distance between magnet and tip is greater a more powerful magnet may be necessary If alnico is used the polarity of the tip of the tube must be determined with relation to the magnet the latter being adjusted to attract not to repel, the tip The tube is passed through the nares into the stomach as usual. After decompressing the stomach by attaching a Wangensteen suction apparatus the tube is passed down to the pylorus To prevent looping back the magnet is applied under fluoroscopic control along the anterior abdominal wall to guide the tip toward the pyloric antrum Once the tip has reached the pylorus the patient is turned to the right anterior oblique position erect or prone and the magnet applied firmly against the right flank posteriorly in line with the general direction of the first portion of the duodenum and at the same level as the tip of the tube as visualized under the fluoroscope The power is then turned on and the tube slowly but steadily advanced from above Under the fluoroscope the tube is seen to pass readily through the pylorus into the first portion of the duodenum The magnet is then removed the tube advanced and the balloon inflated as usual.

Mayer had excellent results in a number of cases, the tube could usually be passed through the pylorus in one or two minutes A new alloy many times as magnetic as alnico offers great possibilities but is not yet obtainable

Critique of Gastroscopy Norman C Tanner[9] analyzes 2 200 gastroscopic examinations made on 1 730 patients of which 470 were repeated examinations made to follow ulcer progress under medical treatment confirm healing observe relapses and confirm doubtful diagnoses The following conditions were disclosed gastric ulcer alone 589 cases gastric and duodenal ulcer 39 gastric ulcer and diverticulum 3 gastric carcinoma 101 gastritis, 267 mucosal tumors 7 submucosal tumors 8, gastric diverticulum alone 2 extragastric tumor, 3 multiple telangiectases of stomach 1 gastric urticaria 1 volvulus of stomach 1 duodenal ulcer 296 duodenal diverticulum 4 cirrhosis of liver 3 and functional or extragastric dyspepsia with normal stomach, 262 Seventy seven gas-

(9) Brit. M. J 2 849 851 Dec 30 1945

troscopies were done following stomach operations and 66 examinations failed or were incomplete

Schindler s instrument was used in the first 950 cases and the Hermon Taylor model thereafter One advantage of the latter is that its introduction through deformed or distorted stomachs is often possible under vision but its use requires more skill than Schindler s instrument and is less suitable in mild kyphosis

Although gastroscopy is supposedly used primarily for diagnosis of gastritis and rarities Tanner has used it most often in diagnosis and observation of gastric ulcer Of 631 such cases 159 were diagnosed by gastroscopy alone despite apparently normal roentgenograms Observations on healing which occurs surprisingly often in hospitalized ulcer patients indicate that the greatest change usually appears early in therapy ulcer size diminishes by contraction of the base so that the edges are brought closer together and radiating folds appear as a result of the smaller circumference The ulcer also becomes more shallow Its size further decreases by new epithelial ingrowth from the edges Healing in acute and subacute and in some moderately sized chronic ulcers occurs in three to six weeks However in many ulcers healing becomes progressively slower There seems to be a limitation to the contraction of the base particularly with complete penetration and epithelial growth is inadequate and too feeble to bridge a wide or deep gap After remaining stationary some of these very chronic ulcers do heal Patients who stop treatment during the stationary period usually return after a year or so with the ulcer in its original condition The importance of gastroscopy in cases of slow healing is that the ulcer can be observed several weeks after roentgenography has shown it apparently healed A mucous bubble hiding a defect in epithelization and scar contractions approximating the edge of a deeply penetrating ulcer may give an erroneous appearance of healing

Gastroscopy should be done if there is uncertainty

tip of the tube of a highly magnetic material alnico which is relatively noncorrosive

Technic—The metallic tip is fixed on the end of an ordinary Miller-Abbott tube; this is used in conjunction with a good hand type of electromagnet. With heavy patients, where the distance between magnet and tip is greater, a more powerful magnet may be necessary. If alnico is used, the polarity of the tip of the tube must be determined with relation to the magnet, the latter being adjusted to attract, not to repel, the tip. The tube is passed through the nares into the stomach as usual. After decompressing the stomach by attaching a Wangensteen suction apparatus, the tube is passed down to the pylorus. To prevent looping back, the magnet is applied under fluoroscopic control along the anterior abdominal wall to guide the tip toward the pyloric antrum. Once the tip has reached the pylorus, the patient is turned to the right anterior oblique position, erect or prone, and the magnet applied firmly against the right flank posteriorly in line with the general direction of the first portion of the duodenum and at the same level as the tip of the tube as visualized under the fluoroscope. The power is then turned on and the tube slowly but steadily advanced from above. Under the fluoroscope the tube is seen to pass readily through the pylorus into the first portion of the duodenum. The magnet is then removed, the tube anchored and the balloon inflated as usual.

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Critique of Gastroscopy. Norman C. Tanner[9] analyzes 2,200 gastroscopic examinations made on 1,730 patients, of which 170 were repeated examinations made to follow ulcer progress under medical treatment, confirm healing, observe relapses and confirm doubtful diagnoses. The following conditions were disclosed: gastric ulcer alone, 5?? cases; gastric and duodenal ulcer, 39; gastric ulcer and diverticulum, 1; gastric carcinoma, 101; gastritis, 2??; mucosal tumors, 7; submucosal tumors, 8; gastric diverticulum alone, 2; extragastric tumor, 3; multiple telangiectases of stomach, 1; gastric urticaria, 1; volvulus of stomach, 1; duodenal ulcer, 206; duodenal diverticulum, 1; cirrhosis of liver, 1; and functional or extragastric dyspepsia with normal stomach, 202. Seventy seven ga

(9) Brit M J 2:840-841 Dec 30 1945

duce certain changes in the mucosa such as blotchy congestion by pressure of the hot lamp bleeding by rubbing with the instrument and superficial erosion or bruise by suction These disadvantages may be overcome by repeating the examination

Phlegmonous Gastritis As Manifestation of Sepsis L J Sachs and Alfred Angrist[1] (Queens Gen'l Hosp Jamaica N Y) report three cases with no mucosal defect in the form of ulcer neoplasm or operative wound One case of marked edema of the stomach submucosa in a patient with meningococcemia with early meningitis is presented as an early manifestation of a phlegmonous inflammation of the stomach One of the three cases of gastritis is given here

Negress complained of severe headache of two days duration pain in back of neck rad ating to lumbar region and anteriorly to abdomen without localization to any quadrant anorexia and weakness without nausea or vomiting Physical examination showed only soft ap cal systolic murmur and slight injection of the pharynx Temperature was 106 F pulse 10_ blood pressure 110/70 She was menstruating Urinalysis showed 1 plus albumin blood showed 3 400 wh te cells with 56 per cent polymorphonuclears _ per cent staff forms and 41 per cent lymphocytes and 3 8_0 000 red cells Hemoglobin was 84 per cent Throat cultures yielded Staphylococcus aureus haemolyt cus and Streptococcus haemolyticus Blood cultures three days after adm ss on and just before death were sterile X rays two days before death revealed marked gaseous distention of the stoma h

The day afte admission whitish exudate with follicles was noted on the left tons l there was slight njection of the posterior aspect of the drum Temperature was 101-103 F for 10 days and then 10_-105 F She became incontinent drowsy and finally comatose and died th fourteenth hospital day She vomited green fluid twice the day before death

At autopsy the stomach was dilated (Fig 88) with firmly adherent yellowish sheets of exudate over the lesser curvature near the cardiac end The stomach wall was th ckened and edematous especially near the card a Rugal folds were well preserved but coarser and mo e rounded than usual Mucosa was dull and granular with scattered areas of congest on espec ally near the cardiac end The sectioned wall showed a soft uniform thick yellow layer which extended from just beneath the mucosa to the external muscle coat

(1) A I t Med 2 563 584 Ap il, 1945

about diagnosis of duodenal ulcer, but only indirect evidence can be obtained This consists of typical thick folds and thick mucosa with prominent areae gastricae, thinning of mucosa in long standing cases and varying degrees of gastritis

In diagnosis of gastric carcinoma gastroscopy is a valuable aid to roentgenography Diagnosis can usually be established after gastroscopic visualization if doubt still exists a second inspection after 10 days of medical treatment usually dispels it In Tanner s series correct diagnosis was made of 13 subsequently confirmed carcinomas which had been considered benign on roentgen examination or had not been examined roentgenographically Although ulcers in the blind areas of the stomach may be missed, carcinomas usually show since they tend to project into the gastric lumen and in early stages have less extragastric fixation than chronic ulcers

Gastroscopic examination after operation on the stomach is always advisable if anastomotic ulceration is suspected After gastrectomy the whole gastric pouch and stoma can be seen After gastrojejunostomy a large part or all of the stoma can usually be seen and even entered with the gastroscope In absence of gastrojejunal ulcer the stoma usually remains open and clear for inspection and jejunal peristalsis can be studied Ulcer of the gastric side of the stoma is usually visible but ulcers on the jejunal side are less often visible because of edema and spasm of the stoma

Diagnosis of gastritis is difficult Gastritis was seen in thick mucosa in 49 cases, 22 of them severe, and in medium thick mucosa in 155 cases In only four of the latter group was it severe enough to cause symptoms With a thin mucosa changes are difficult to observe There were 63 cases of gastritis in a thin or atrophic mucosa 39 of them severe In 27 cases of gastritis there were associated erosions many of them being seen after gastroduodenal hemorrhage

The instrument and method of gastroscopy may pro

numerous conditions may produce this picture a flat plate x ray seems to be indicated in such cases History or physical examinations in the other two cases also did not suggest the condition diagnosis was not made clinically in any case There was no instance of pre existent mucosal defect such as carcinoma ulcer or operative wound which could be considered a portal of entry for invading organisms suggesting the direct route of infection In the second and third cases infection definitely occurred via the blood stream even though chronic gastritis was present in the latter In the first case the one reported here the possibility of direct infection by swallowing of organisms cannot be excluded entirely but absence of a portal of entry in the stomach mucosa favors the hematogenous route The authors report a fourth case of phlegmon of the gallbladder which illustrates the hematogenous route of infection and closely resembles the described cases of phlegmonous gastritis Phlegmonous gastritis is therefore considered a manifestation of sepsis with localization in the stomach wall rather than a lesion following local invasion from the lumen

[Happily this grave disorder is infrequent and the diagnosis is rarely made ante mortem —Ed]

Lesions of Gastric Mucosa in Pernicious Anemia S W Olson and F J Heck report autopsy studies on 94 cases of pernicious anemia in 41 of which gastric tissues were examined Sections taken during routine autopsies from stomachs with no gross lesions were studied for comparison Many showed evidence of residual lesions of ulcerative gastritis consisting of varying degrees of thickening and irregularity of the muscularis mucosae collections of lymphocytes atrophy of specialized cells and disorganization of mucous glands Most sections showed some acid cells Sections of gastric tissue in the pernicious anemia cases showed many of these same residual lesions except that the mucosal layer was thinner atrophy of the

(2) P St ff M t M y Cl 0 74 78 M 7 1945

This process, although diffusely involving the entire stomach wall diminished in intensity and extent toward the pylorus Microscopically the mucosa was intact without ulceration There were some inflammatory infiltration and marked congestion The submucosa showed diffuse edema and fibrinous exudate extensive inflammatory infiltration lymphangitis and venous thrombosis In the muscular coat the exudate was more compact and there were more marked abscess like areas with marked lymphangitis The serosa was edematous with some inflammatory cells and involvement of lym



FIG 88 —Gr s ppe r nce of toma h w ll thickened by dema a d e udate muc al f lds p m n nt Note b enc f nvolvement of sophagus and du d n m

phatics There were also early peritonitis left pleural and pericardial effusion and acute hyperplastic splenitis Postmortem cultures of the peritoneum showed Bacillus coli and of the left pleura Bacillus coli Bacillus pyocyaneus and nonhemolytic streptococcus. Final anatomic diagnosis was diffuse phlegmonous gastritis with extension to the duodenum early peritonitis plural effusion on the left pericardial effusion acute hyperplastic splenitis and serous hepatitis

History and physical examination offered little or nothing to suggest diffuse phlegmonous gastritis it probably appeared later The marked gastric dilatation on the x ray film is noteworthy Although this dilatation is not pathognomonic of diffuse phlegmonous gastritis and

the stomach area Greater incidence of cancer in the pyloric gland region in young people noted by Torgersen at autopsy in 400 unselected cancer cases conforms with the fact that gastritis originates in that region and gradually spreads orally with a more even distribution of cancer throughout the stomach in elderly persons Most authorities agree that gastric cancer originates not in a healthy but in a pathologic gastritic mucous membrane It would therefore be of interest to investigate whether gastritis exists which is situated mainly in the region of the fundus glands and if so if cancer has a corresponding localization

In pernicious anemia gastritis is usually localized to the region of the fundus glands whereas changes in the pyloric gland region are rare unless the disease is of long standing In view of this cancer in these patients should be found more frequently in the region of the fundus glands Torgersen found 90 cases in the literature and observed 16 in which cancer localization was fairly well determined In 33 the cancer was in the pyloric gland region and in 66 in the fundus gland region Of the 66 cancers 27 were on the side of the greater curvature and 7 infiltrated the entire stomach Thus the region of the fundus glands is more frequently involved in pernicious anemia than in cancer generally Distribution of cancers in pernicious anemia follows distribution of gastritis as in the case of ordinary cancer This is of particular interest since gastritis is the primary lesion in pernicious anemia and cannot be considered a sequel to cancer Thus these facts support the opinion that gastritis plays a primary role in causation of cancer

[The greater nc dence of ga tric carcinoma in patients with pernic ous anemia is now generally recogn zed It behooves us to keep pernic ous anemia patients under treatment and to make periodic roentgenoscopic examination of the stomach whether or not gastric d sturbances are manifest —Ed]

Chronic Gastritis and Carcinoma of Stomach Shields Warren and William A Meissner[4] (Harvard Cancer

(4) G t te l gy 3 51 256 Octob 1944

specialized cells was almost complete there were fewer glandular tubules and hyperplasia of the mucous glands was common This hyperplasia consisted of irregularity of cell size and of nuclear size and position hyperchromatism of nuclei formation of irregular, abnormal appearing glands and mitotic figures

Whether such degrees of hyperplasia may produce stomach carcinoma is difficult to prove Carcinoma of the stomach was present in 2 of the 63 untreated cases of pernicious anemia A gross lesion was present in 5 and carcinoma in situ in 1 of the 31 specifically treated cases, in 2 of these, carcinomas of grades 1 and 2 were present, and in the remainder, carcinomas of grade 2 This suggests a tendency toward increase in number of cases of carcinoma in this small series Incidence of benign polyps also was increased in the treated group, in several cases there were both benign and malignant polyps The increased longevity of pernicious anemia patients treated specifically probably accounts partly for increased incidence of polyps and carcinomas of the stomach as the processes active in alteration of the gastric mucosa thus also continue for many years

Thus pernicious anemia is a disease of the gastric mucosa as well as of the hematologic and neurologic systems Treatment sufficient for maintenance of normal blood may not be adequate to prevent atrophic changes in the gastric mucosa

Localization of Gastritis and Gastric Cancer, Especially in Cases of Pernicious Anemia Johan Torgersen[3] (Univ of Oslo) studied 506 gastric cancers 106 from patients with pernicious anemia According to all extensive statistical reports, cancer is found most frequently in the region of the pyloric glands and is rarest on the side of the greater curvature i e, the fundus glands Gastritis also is most frequent in the region of the pyloric glands These facts are particularly notable because the region of the pyloric glands occupies only one fourth of

(3) Acta radiol. 25 845 855 1944

submucosa the so called follicular gastritis Increased vascularity edema and hyperemia are often present Epithelial changes consist of alteration probably progressive of the mucosal cells from normal There are excessive formation of mucus diminution in number of chief and parietal cells formation of atypical glands often cystic (Fig 89) and formation of atypical gastric cells which appear embryonic and often approach ap



Fig 90—Tw l nd f ll d t t al ep th l m ed ed f m × 33

pearance of intestinal epithelium (Fig 90) There is an increase in number of mitoses in the neck region of the glands

In severe stages of chronic gastritis the epithelium undergoes alterations comparable to premalignant lesions in the cervix breast and skin The most important changes are atypical cells atypical glands and increased mitotic activity When complete epithelial changes have occurred reversal to normal epithelium is probably impossible This change is often seen in so-called atrophic gastritis Only the severe stage of chronic gastritis with these marked epithelial alterations shows the necessary

Commission) studied 356 stomachs which were com pletely or partially removed for primary gastric car cinoma or for peptic ulcer of the stomach or duodenum

Diagnosis of gastritis must not be made solely on the finding of scattered inflammatory cells in the gastric mucosa consisting chiefly of lymphocytes and plasma cells these cells are normally present and were the only finding in many of the stomachs particularly those re



FIG 89 —Atyp al glands lined by lls h wing f eque t m toses red ced from X 33

sected for duodenal ulcer Exudative and epithelial changes are found in chronic gastritis Exudative changes are the more frequent and occasionally are ex tensive whereas epithelial changes are slight They con sist of infiltration of the mucosa and submucosa by in flammatory cells and in more severe stages of fibrosis particularly of the muscularis mucosae Inflammatory cells are mainly lymphocytes and plasma cells occasion ally with some eosinophils mast cells and polymorpho nuclear leukocytes The earliest and mildest stage con sists of an increased number of these cells later intense infiltration occurs often with lymphoid follicles in the

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criteria for premalignancy, mere presence of mucosal infiltration by inflammatory cells and slight alterations of epithelium is not sufficient

Gastric Mucosal Atrophy and Carcinoma of Stomach Arthur Purdy Stout[5] (Columbia Univ) studied 150 stomachs, 50 with gastric carcinoma, 50 with gastric ulcer and 50 without gastric ulcer or carcinoma which had been removed because of duodenal ulcer Histologic features selected for special analysis were (1) transformation of gastric mucosa into a mucosa of the intestinal type commonly called intestinal metaplasia (2) loss of characteristic gastric glands with their chief and parietal cells in the fundus and their replacement by a mucosal pattern characteristic of the pylorus and antrum, called pylorization of the fundus and (3) development of microscopic mucosal cysts

Intestinal metaplasia and pylorization of the fundus were found in 50 per cent of the stomachs with duodenal ulcer 60 per cent of those with gastric ulcer and 94 per cent of those with gastric cancer The degree of involvement tended to be much greater in the last named group The three groups were strictly comparable as to sex but not as to age there being an ascending progression in mean ages of the three groups There was a steady increase in incidence and size of area of mucosa involved from the third decade when it first appeared to the eighth decade when every stomach showed considerable involvement suggesting that atrophic changes are found in the stomach with increasing frequency with advancing years until in old age possibly every stomach shows some evidence of mucosal atrophy

Mucosal cysts and cystic dilatation of the glands were much more frequent in stomachs with cancer than in those without cancer this feature became increasingly frequent with advancing age but was disproportionately greater in stomachs with carcinoma Individual cases indicated that the solitary sporadic cysts occurred usu

(5) New York State J Med 45 973 977 May 1 1945

ally without any demonstrable relation with carcinoma but that most of the stomachs with frequent mucosal cyst formation also had cancers and that the cysts sometimes were more numerous in the vicinity of the carcinoma The study suggested that there was a certain degree of cellular disturbance in the immediate vicinity of some carcinomas one feature of which was development of cysts Rarely a cyst was found lined partly with can cerous and partly with noncancerous cells but even these phenomena cannot be considered proof of development of carcinoma from a cyst and the exact relationships between atrophy of the gastric mucosal epithelium cyst formation and gastric carcinoma are undetermined

Gastric Diverticulum Gastroscopic Observation of Two Cases Frank Whitehouse and J M MacMillan[6] (Percy Jones Gen l Hosp Battle Creek Mich) report three cases in two of which gastroscopic examinations aided in diagnosis and treatment Case 3 is given here

Man 26 had hematemesis during fever therapy for sulfonamide-resistant gonorrhea. Po ntgen and roentgenoscop c examinations showed a diverticulum of the stomach Gastroscopic examination 10 days after hematemesis showed the diverticulum in the cardia and on the posterior wall. The mucosa l ning the diverticulum was well visualized and appeared normal The edge of the diverticulum was flat and sharply defined when the stomach was well inflated but when nflation was not so complete the edge was rolled and raised with rugae running up to the margin (Fig 91) Two black pigment spots about 1 cm were noted 5–6 cm from the diverticu lum it was assumed that the hemorrhage had come from the s te of these spots The mpression was that the hemorrhage followed ingest on of a large dose of sulfonamide at the time of fever therapy with added factors of retching and vascular changes inci dent to fever therapy There was no history of gastric trouble or of blood dyscrasia Four months later there had been no recurrence of hemorrhage or onset of gastro intestinal symptoms

The authors feel that in certain cases,with hematemes is gastroscopic examination can be done soon after hemorrhage with safety In this case it was delayed for 10 days because of severe herpes simplex of the lips Any patient with a diverticulum of the stomach for

(6) G stro te l gy 3 13 J ly 1944

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with it were bands of muscle tissue representing remains of the inner longitudinal layer Many fibers showed fibrinoid degeneration The submucosa was composed of dense collagenous tissue The circular muscle was almost completely replaced by fibrous tissue isolated fibers persisting as islands lying in edematous fibrosed and vascularized areas The longitudinal fibers were few thin and atrophic The serosal layer was edematous and fibrotic (Fig 9~) The stomach seemed to be well preserved The mucosa of the jejunum



Fi 9 (l ft) —C 1 Esoph gu w th fibrill m terial n muco l su f th ck fib t subm sa d t n fib epl m nt f m scle l y Tr h m t n d ed f om × 31
Fig 93 (ght) —S m S t f int st w th nly n rrow b d f fib ou t j g mu sa d fib t th ckened se Tr h m st n × 30

showed diffuse lymphocytic infiltration. The villi enclosed masses of hemosiderin The submucosa contained many dense collagen fibrils but was not thickened Both muscle layers were atrophied. In many places the muscle layer was so extensively replaced by bands of fibrous tissue that the mucosal surface was in close approximation with the serosa The mucosa and submucosa of the appendix we e hyalinized and the lumen reduced The vessels were greatly thickened and hyalinized The muscularis was atrophic The changes in the colon we e similar to those in the small intestine The lesions we e patchy The vascular changes in the gastro intestinal tract were slight but the serosa was fibrotic and thickened throughout (Fig 9) Anatomi d agno es included generalized scleroderma acute fib nous and chronic pericarditis fibrosis of the endocardium and myocardium bilateral pleural effusion ascites edema of the feet diffuse glomerular and arterial lesions of the kidneys muscular atrophy of the gastro intestinal tract degenera

whom operation is contemplated should first be considered for a gastroscopic examination particularly if the diverticulum is in the lower two thirds of the stomach. Most diverticula are on the cardia and posterior wall and



Fig 91

these are generally least likely to be significant They can be visualized without danger if clinical judgment warrants gastroscopy

Pathology of Scleroderma with Special Reference to Changes in Gastro Intestinal Tract Margaret Bevans (Columbia Univ) reports two cases of generalized scleroderma with unusual gastro intestinal changes and various other lesions in addition to dermal alterations The changes were more severe than clinical course and laboratory data indicated.

CASE 1—Post mortem examination showed that throughout the esophagus the mucosal layer was replaced by fibrillar, acellular tissue with a few adherent red cells Beneath and sometimes mingled

( ) Am J Path 1 ?5 41 January 1945

hibited evenly rounded surfaces covered by intact movable mucosa although in some cases large craters were visible The hemangioma was softly indented with typical accumulations of phlebolites in the cavernous spaces Movability of the tumor in relation to the mucous membrane and muscular wall compressibility of the soft tumors and appearance of peristalsis and relief outline of the neighboring mucous membrane are aids and indications to correct diagnosis

In most cases differential roentgen diagnosis between carcinoma and benign tumor is difficult Infiltration of the mucous membranes indicates a carcinoma since this change does not occur in benign tumors Operative findings likewise sometimes do not permit differentiation between malignant or benign growths especially in the case of papilloma only microscopic examination can give the final diagnosis

Forssman points out the relatively common occurrence of malignant proliferation especially in cases of papillomas and simple polyps In a few cases gross examinations of specimens during and after operation disclosed no signs of malignancy and diagnosis of malignancy based on microscopic examination came as a surprise

Peptic Ulcer in Adolescence Relation to Pituitary Dysfunction Asher Winkelstein[9] studied 24 cases in the puberty adolescent class All had duodenal ulcers agreeing with the general impression that gastric ulcer is found in older patients Most of the 24 were between 12 and 15 3 were 17 and 1 was 11 Symptoms generally were severe five patients had massive hemorrhages and there were three perforations Eleven had partial gastrectomies The most striking feature was that simultaneously with onset and early course of the ulcer symptoms the boys grew rapidly 10 grew to 6 ft 9 to 5 ft 11 in and 5 to 5 ft 9 in All were thin This association of rapid growth with peptic ulcer may be

(9) J Mt S n i H sp 1 773 775 M y-J 1945

tion of the esophageal mucosa minimal pulmonary fibrosis multiple decubitus ulcers muscular atrophy atrophy of the thyroid and partial degeneration of the optic nerve chiasm and tracts

CASE 2 —Postmortem examination showed the entire stomach wall less than half normal thickness The muscularis mucosae was thin and in many places replaced by fibrous tissue and the submucosa was composed largely of coarse connective tissue fibers Muscle layers were atrophic and serosa was slightly thickened. The submucosa of the intestines contained numerous coarse connective tissue fibers The muscularis mucosae was occasionally thinned. Marked edema separated the muscle layers In many places the muscle layer was replaced by fibrous bands in both circular and longitudinal layers The peritoneum was thickened its blood vessels were dilated and congested Infiltration of lymphocytes extended from the peritoneum into the surrounding fat tissues The intima of some larger arteries was thickened and the arterioles shared the edema of the surrounding tissues Anatomic diagnoses included generalized scleroderma necrotizing and proliferating arteritis pulmonary fibrosis bilateral hydrothorax dilatation of the heart mild coronary sclerosis myocardial fibrosis chronic passive congestion of the liver diffuse glomerular and arterial lesions of the kidney atrophy of the thyroid atrophy of the intercostal muscles and muscular atrophy of the gastrointestinal tract

Roentgen Diagnosis of Benign Gastric Tumors Gösta Forssman[8] (Stockholm) discusses 30 cases of benign gastric tumor, found between 1930 and 1940 either at operation or at roentgen examination 11 cases of simple polyp 6 of polyposis 3 of papilloma, 8 of myoma, 1 of neurinoma and 1 of cavernous hemangioma Two thirds of the cases were in women and most patients were aged 46–70 the hemangioma occurred in a patient aged 19 and one case of polyposis in a patient aged 20

Roentgen diagnosis of polyps is not difficult, since they appear as sharply limited round movable filling defects in a soft mucosa but malignancy cannot always be excluded *Thus in one case a soft pedunculated polyp* was visible on the side of the greater curvature after using compression the polyp was excised and nothing suspicious was noted Microscopic examination, however revealed beginning malignancy The papillomas showed papillomatous surfaces while the myomas ex

(8) Acta di 1 24 135 165 1943

eral circulation many dissimilar conditions such as disease injury and nutritional deficiencies may contribute to the genesis of ulcer through alterations in circulatory efficiency The periodicity of ulcer symptoms and psychogenic factors suggest dysfunction of intrinsic control of blood composition or of blood flow as a possible factor in initiating or augmenting peripheral vascular deficiency in this condition The authors investigated peripheral circulation in peptic ulcer by studying systolic and diastolic blood pressure and pulse rate of 40 men with x ray evidence of chronic duodenal ulcer at monthly intervals Significant cyclic fluctuations in the components of the two systems were observed A downward trend initiated in spring with minimal values in summer and early autumn was observed for systolic and diastolic blood pressure pulse pressure pulse rate and hemoglobin hematocrit total serum protein albumin and globulin levels The cycle was reversed in autumn and winter None of the patients had ulcer exacerbations but it is of interest that spring and autumn periods of transition are also the periods of increased ulcer activity Lowest yearly levels of pulse pressure and serum albumin occurred in late summer and early autumn suggesting that the time of greatest incidence of hemorrhage from ulcer namely autumn is preceded by a period of decreased circulatory efficiency marked by relatively lowered cardiac output and decreased colloid osmotic pressure of the blood plasma

[There is no convincing explanation for the cause underlying periodic or seasonal exacerbations of gastroduodenal ulcer This investigation has been one of several serious attempts to unravel the mystery Perhaps the solution will elude us until we know the actual cause of ulcer —Ed]

Civilian Dyspepsia F Avery Jones and H Pollak[2] report that of 1 522 dyspeptic patients seen at one London hospital 952 had peptic ulcer Ratio of women to men with peptic ulcer was 1 4 7 Ratio of gastric to

(2) B i M J 1 797 800 J 9 1945

only a coincidence and larger groups must be studied to establish statistical validity However there is possibility of a ductless gland relation At adolescence the sex hormones come into play and the growth hormone is elaborated by the anterior pituitary Previous experiments with dogs showed that ulcerations around abdominal wall gastric pouch orifices increased during lactation During estrus acid secretion lessened and ulcerations healed Such observations indicated a possible relation of the anterior pituitary gland involved in lactation, to the increased acidity and ulceration Peptic ulcer is predominately a male disease It is mild in females in whom it often begins at the natural or artificial menopause and has severest manifestations at or after the menopause Estrogens may relieve menopause ulcer symptoms

These facts indicate that the rapid growth and peptic ulcer in boys may be associated with some abnormality in function of the anterior pituitary gland Acromegaly was not present in any case Another possible etiologic factor may be the psychologic and emotional disturbances common during adolescence However this feature was not prominent in the group of boys except for one who was extremely resentful against his parents

[An interesting observation if a larger series of patients bears this out I have seen a number of adolescents and younger children with verified ulcer in whom evidence of pituitary dysfunction was not apparent Perhaps I wasn t observant enough But in such individuals as in young college folk with hypertension the immediate forebears or siblings were often afflicted with the same disorder — Ed]

Chemical Composition of Blood and Some Cardiovascular Reactions in Chronic Peptic Ulcer throughout One Year Helena F Riggs Russell S Boles John G Reinhold and Paul S Shore[1] (Philadelphia Gen l Hosp) suggested previously that prolonged or repeated disturbances of peripheral circulation form the essential background of peptic ulcer Since changes in blood composition or in mechanics of blood flow influence periph

(1) Gastroenterology 3 480 489 Decemb 1944

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(1) G t at r I gy 3 480 489 Dec mber 1944

ulcer is greater than that from duodenal ulcer Mortality rate among men for both types of ulcer differs widely in different social classes Under 55 death from gastric ulcer appears to be associated with low economic status At the same ages in the case of duodenal ulcer there is no significant class bias In old age deaths from both gastric and duodenal ulcer are greater among the well to-do Mortality is higher in the Greater London area than elsewhere in England and Wales and in general is lower in rural areas The pattern of gastric ulcer mortality strongly resembles that of gastric cancer mortality The acute depression of the 1930s followed by re employment is reflected in the behavior of peptic ulcer mortality Heavy air attacks of 1940–41 resulted in a sharp rise in mortality rate for duodenal ulcer, followed closely by a similar rise in mortality rate for gastric ulcer

Some Aspects of Peptic Ulcer during Wartime V M Kogan Yasny[4] points out that war conditions both at home and at the front produce intense trauma nervous tension and emotional strain thereby disturbing the autonomic nervous system Peptic ulcer is a disease of the neurohumoral mechanism in which the vegetative nervous system and glandular apparatus of the stomach play a special part Psychic and physical trauma with improper eating accelerate appearance of the clinical manifestations Nicotine also plays a part in development and complications of ulcer Spread of the disease to the entire warring world especially among young people the increased incidence of the disease among women and children and the occurrence of ill defined forms permit use of the term wartime peptic ulcer

With peptic ulcer there are serious metabolic disturbances These include disturbances of acid base balance and pyloric function disturbances of liver function and carbon oxygen exchange leading to spontaneous postoperative hypoglycemia and vitamin metabolic

(4) Kli med. 2 12 15 1944 Am Re S t M d 233 237 F bru ry 1945

duodenal ulcer was 1 2 5, higher than in any previous series of patients in London One explanation may be that patients with duodenal ulcer probably have less chance of hospitalization than those with gastric ulcer In military series the ratio of gastric and duodenal ulcers was similar to that for males under 45 in this civilian series Calculations suggest that about 1,500,000 persons in England and Wales have had peptic ulcer

Relapse of peptic ulcer is common, and most of those who have had ulcers must continue dietary regimes to avoid further symptoms e g , regular meals with bal anced diet avoidance of indigestible foods and fatigue and maintenance of a calm, philosophical attitude This problem mainly confronts men during their working life and often during their prime Although peptic ulcer has low mortality, causing little more than 1 per cent of nonviolent deaths, it causes much suffering and incapacity for work, which is particularly unfortunate because the usual ulcer personality is one of aggressiveness and endurance The man with duodenal ulcer is usually of special value to industry, for he is over conscientious with plenty of drive and a sense of good standards of work the problem should therefore be studied more intensively, especially the relation of the peptic ulcer patient to industrial life

Epidemiology of Peptic Ulcer J N Morris and Richard M Titmuss[3] report vital statistics for England and Wales covering mainly the period between 1921 and 1941

Among men mortality from peptic ulcer is steadily increasing In 1939–41 this rise was accelerated Among women, except in old age mortality has been decreasing, in 1939–41 there was some reversal of this trend The important increase is in the death rate for both gastric and duodenal ulcer in men over 45 The rate in young women has now almost reached zero Among both men and women at all ages mortality from gastric

(3) Lancet 2 841 845 Dec 30 1944

sion and administration of vitamins A B C D and K and large quantities of calcium are recommended When pain is prolonged and severe atropinization should be used as well as the so-called bilateral block of Vishnev sky and Speransky X ray therapy occasionally is pal liative In chronic conditions and tissue defects such as a niche good results are attained by neutralization of acidity and use of stimulating therapy in the form of antireticular endothelial cytotoxic serum of Bogomolets

Incidence of Peptic Ulcer at St Thomas Hospital 1910–37 *Henry Tidy[5] examined admissions for peptic* ulcer to obtain an indication of the trends Analysis of available records indicated that a division must be made between gastric and duodenal ulcer with subdivisions for sex and age

Admissions for gastric ulcer in males over 40 in creased rapidly between 1925 and 1930 the rise then ceased but the maximal rate was maintained The trend for males under 40 was somewhat similar but incidence was much lower The rise was less marked in the group under 40 Duration of symptoms previous to admission was comparatively constant for the two age groups and suggests that the older group was composed not mate rially of males with a continuation of symptoms arising at an earlier age but of those with new ulcers

Admissions for duodenal ulcer in males rose irregu larly and moderately after World War I until 1929–30, then fell to the level of 1910–13 The two age groups were similar in number of admissions and trend As compared with the gastric ulcer group there were pro gressive increase in duration of symptoms and an in creasing proportion of patients with a history of symp toms of long duration Admissions for duodenal ulcer commonly exceeded those for gastric ulcer until 1926 The curve for gastric ulcer in males over 40 then passed the corresponding curve for duodenal ulcer and rose far above it The curve for gastric ulcer in males under 40

(5) B M J 1 319 3 4 M 10 1945

disturbances, which during wartime assume the character of a definite avitaminosis such as pellagra and scurvy The peculiar features of wartime peptic ulcer are severe acute symptomatology unrelieved for long periods and frequently disappearing without leaving organic gastric changes prolonged hemorrhages which frequently assume the form of a hemorrhagic diathesis with vitamin C and K deficiencies as contributory factors in the etiology of ulcer when dystrophy is present, protracted healing of the niche and tissue defects frequent penetrations and sudden perforations without previous history unusual size of the lesion which occasionally is as large as a fist and resembles a malignant lesion more frequent transition into malignancy (8 per cent before and 15 per cent since the war), prolonged pylorospasm frequent and prolonged loss of earning capacity and difficulty in differentiation between benign and malignant lesions

The following indications are recommended for surgery (1) perforations, (2) stenosis, (3) degenerations (4) bleeding ulcers not amenable to conservative treatment (5) symptoms and a niche which do not disappear after prolonged medical therapy, (6) loss of earning power over prolonged periods and (7) complications following surgery In doubtful cases surgical and medical consultation may decide the best procedure With multiple erosions and bleeding resembling hemorrhagic diathesis an ascorbic acid deficiency may be the etiologic factor transfusions and parenteral administration of vitamins C and K may save the patient from operation

Individualized treatment of wartime ulcer is necessary The regime should consist of physical and mental rest, abstinence from smoking and a well balanced diet with special attention to proteins and vitamins Parenteral administration of amino acid and vitamins B C and K is recommended When bleeding is acute the author prefers transfusion In small hemorrhages transfu

monly at different ages and differently in the two sexes For duodenal ulcer there are no such differences between the age groups which suggests that the same set of factors operates at all ages but with widely different effects on males and females Psychoneurotic stimuli often appear to be the exciting cause of development of duodenal ulcer and of perforation However this theory does not explain the rarity of duodenal ulcer in women and the even greater rarity of perforation The severest air raids scarcely altered the curve for perforations in women but sent the curve for men to a high level Nor is the theory consistent with the practical absence of duodenal ulcer before 1900 and its subsequent trends Some independent predisposing cause is indicated psychoneurotic stimuli may pull the trigger

Experiences with Peptic Ulcer in an Army Station Hospital Louis Zetzel[6] (Camp Polk La) reports on 130 ulcer patients of whom 5 had gastric and 126 duodenal ulcers. About 90 per cent had a definite history of ulcer for an average of six years before induction Six patients had massive bleeding from the upper gastrointestinal tract all of whom were treated with a modified Meulengracht regimen A few required transfusions Six patients were treated for perforated ulcer all but one being operated on within 12 hours operation consisted of repair of the perforation There was no mortality in the entire series All patients were ultimately discharged

Treatment of uncomplicated peptic ulcer consisted of a strict Sippy regimen usually during the first five days with milk and cream given on the hour during waking hours in addition to mild sedation and tincture of belladonna Complete bed rest was enforced Thereafter there was a gradual increase in the diet so that after 10 days nearly all patients were on a fourth stage Sippy diet All patients were given group instruction about their disease and the more common factors associated with exacerbations and graphic representations of its patho

(6) G t t l gv 3 472 479 D mb 1944

passed the corresponding curve for duodenal ulcer in 1929

The trends of admission for gastric ulcer in females were completely independent in the age groups under and over 40 The only group of considerable size in recent years was that of gastric ulcer over 40 There was a steady but moderate increase in admissions to a maximum in 1930 with a subsequent fall All other groups of peptic ulcer are now rare in women Incidence under 40 is low and the mean age which before 1913 was below that for males is now higher

The proportion of patients admitted with perforations was higher for duodenal than for gastric ulcer For duodenal ulcer, the proportion was the same in the two age groups but for gastric ulcer it was higher under 40 Case mortality rate for all ages was higher for gastric than for duodenal ulcer owing to the high case mortality for gastric ulcer over 40, which was three times greater than for gastric ulcer under 40 Case mortality rate for duodenal ulcer was the same in both age groups These differences between perforations in the two age groups for gastric ulcer together with the other differences indicate different etiologic factors at different ages For duodenal ulcer there were no such differences The proportion of patients admitted with perforation was lower in females than in males in both ulcer groups Perforations in women are now rare Thus it appears that in women development of ulcer is comparatively rare and when present an ulcer has a low liability to perforation Possibly the factors which determine formation of an ulcer and perforation are not identical

The etiologic factors of gastric and duodenal ulcers are concededly different There are differences in the trends of the death rates for the two types in England and between England and Scotland and differences in the standardized mortality ratios for the five major social classes There may be more than one group of etiologic factors producing gastric ulcer operating com

particularly from younger men with symptoms of short duration Antacids were used for relief from pain in only 18 per cent of cases but many patients were already improving when they came to the hospital

The psychosomatic features and their management and the disposition of ulcer patients in the Army are of particular importance In many cases there was remarkable coincidence between onset of distress and some unpleasant episode Some patients were allegedly asymptomatic until the day of induction There was remarkable subsidence of previously refractory distress in some patients when discharge from the Army seemed assured On the other hand there was recrudescence of distress often with added symptoms not previously shown in patients who had to return to duty The aggressive driving conscientious punctilious perfectionist type of personality commonly observed in civil life was seen relatively rarely in soldiers with peptic ulcers slovenly seemingly placid unobtrusive slow moving men were seen oftener There was a surprising number of ulcer patients with low grades of intelligence and the intellectual attainment of many of them was extremely limited

Hemorrhage occurred in 17 7 per cent of 225 cases perforation in 7 6 per cent and pyloric obstruction in 3 1 per cent

[The foregoing two contributions by capable American observers on the basis of a large personal experience in military hospitals are highly instructive The provocative role of personality disorders or emotional stress has been appropriately stressed The demeanor of the civilian anxious to escape military duty in contrast to that of the professional soldier is a common observation in all armies irrespective of nationality Be k and F edman s observations on the type of ulcer personality encountered in the Army suggest that it is usually in direct contrast to that observed in civil life —Ed]

Large Melena of Obscure Origin Harvey B Stone[8] (Baltimore) reports 21 cases with symptoms of massive hemorrhage passed by rectum of obscure origin Analysis permits classification into three groups Group 1

(8) A S g J 0 58 597 O t be 1944

genesis Individually an effort was made to determine the relative importance of diet fatigue illness and emotional tension the last almost always deeply repressed Use of the word cure was discouraged and the concept of relief compatible with a relatively normal existence in civilian life was emphasized as the natural sequel of co operation

Peptic Ulcer Problem in the Army J Edward Berk and Alexander W Frediani[7] (Tilton Gen l Hosp, Fort Dix N J) report on 340 patients with peptic ulcer *About 74 per cent had symptoms indicating existence* of ulcer prior to induction duration of symptoms varied from 8 weeks to 20 years Length of service before first hospitalization in the Army averaged 7½ months In contrast to the rapid appearance of ulcer distress in inductees is the group of regular Army personnel in the series whose average duration of service before first hospitalization for ulcer was 4 2 years Average number of hospitalizations before admission to Tilton General Hospital was 1 7 for inductees and 2 for regular Army personnel About one fourth of the regular Army personnel *had been returned to duty before July 1943 all* inductees with peptic ulcer were discharged but since then restricted duty had been given to soldiers with uncomplicated ulcers whose symptoms first appeared while in the service or who possessed skills useful to the Army

Average age was 29½ There were 4 4 per cent Negroes and 4 per cent Jews In 309 cases in which accurate records on location of ulcer were available there were 310 ulcers of these 303 were duodenal 6 gastric and 1 jejunal Roentgen signs of ulcer were seen in all but 1 of 225 cases however an ulcer niche or crater was seen in *only 28 8 per cent Fractional Ewald meal* gastric analysis disclosed hyperacidity in 54 2 per cent of the 225 cases Abnormal motility was present in 36 per cent of 211 cases, hypermotility in 8 5 per cent and hypomotility in 27 5 per cent Atypical ulcer histories were obtained

(7) Gastroenterology 3 43 44 December 1944

[This is a timely contribution The profession as a whole is too quick to conclude that a gastro-enteric hemorrhage means ulcer The disconcerting fact remains that frequently the cause of such hemorrhage is obscure I am sure that most of my readers with a large gastro-intestinal hospital service will agree with me I have had under observation at least 10 such cases in the past month In the absence of symptoms or signs of ulcer one must be circumspect even though hemorrhage occasionally is the sole manifestation of ulcer In the presence of symptoms more or less characteristic of ulcer one must assume presence of an ulcer or a mucosal lesion until proved otherwise At times a duodenal ulcer or duodenitis or a shallow chronic gastric ulcer escapes detection by the most expert roentgenologist especially in the early stages Gastroscopic examination is also indicated in such circumstances Hematemesis with or without melena implies presence of a lesion in the esophagus stomach or upper reaches of the duodenum to the exclusion of the small bowel or proximal colon Melena alone in absence of gastric symptoms or signs requires exclusion of a tumor in the small intestine or a bleeding ulcer in a Meckel diverticulum Acute ulcers that bleed readily heal and leave no trace and even scurvy must be considered as possibilities My most recent case of severe hematemesis was in a young man in otherwise vigorous health and with no significant gastric disturbances His physician promptly concluded that he had a peptic ulcer and treated him on this basis *However careful roentgenoscopic examination failed to visualize* a gastroduodenal lesion but fortunately demonstrated extensive varicosities of the lower two thirds of the esophagus And yet significant symptoms or signs of hepatosplenic disease the usual underlying cause of such disorder were conspicuous by their absence. And so it goes —Ed]

Indications for Surgical Treatment of Peptic Ulcer Carl G Morlock[9] (Mayo Clinic) points out that important etiologic factors of duodenal ulcer are excessive acidity of the gastric contents and neurogenic constitution The typical dynamic aggressive high strung personality often noted in such patients always antedates symptoms of ulcer and may be aggravated by onset of pain Psychoneurologic symptoms include hyperirritability tenseness anxiety restlessness sensitivity and emotional instability Personality adjustment to overcome this tense nervous background is one phase of therapy Other causes are infection trauma and faulty nutrition All factors must be considered before decision regarding medical or surgical treatment and each case must be individualized

(9) J 1L t 65 8 1 J ry 1945

contains cases in which a definite cause of bleeding could be found group 2 cases in which a lesion was discovered which could be the cause of the bleeding, and group 3 cases in which no cause could be discovered after complete search and analysis. Existence of this last group offers a conclusive reason why early operation should not be performed Often many of these patients never bleed again others may have another hemorrhage after a long time in one case after 20 years Still others may have recurrent hemorrhages a number of months apart In these last cases exploratory operation may be justified to discover a lesion which could not be found in previous studies The following conditions may cause such bleeding tumors of various types especially polyps and hemangiomas less often malignant growths gastric duodenal intestinal and colonic ulcers and ulcers in Meckel s diverticulum diverticulosis regional ileitis and colitis vascular lesions such as varicose veins infarctions and miliary aneurysms trauma from ingested foreign bodies erosions from pressure of extra intestinal lesions such as aneurysms of large vessels and constitutional causes such as blood dyscrasias and hypertension.

In immediate treatment of a large hemorrhage morphine injection is probably useful Transfusion of whole blood is given if indicated the blood must be given slowly and not in larger quantities than 500 cc All food by mouth is stopped and only small amounts of water are allowed Intravenous fluids sufficient to maintain water balance are given Inclusion of plasma in such fluids appears to be of help Bleeding usually stops within 48 hours and the patient is rapidly rehabilitated from the early low level of the initial shock As much as two or three weeks may be needed for complete restoration and before diagnostic study is permitted This study consists of careful history taking gentle abdominal examination and rectal palpation which may be done sooner then sigmoidoscopic examination barium enema and gastro intestinal roentgen studies and blood studies

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Subtotal Gastrectomy in Medically Resistant Ulcers J William Hinton[1] (New York City) reviews statistical analyses which indicate that if there is a dictum for treatment of ulcers it should be more mistakes are made by too early rather than by too late surgery About 90 per cent of the ulcers diagnosed within the first year of onset of symptoms can be satisfactorily managed on a medical regimen if the patients can be convinced of the value of co operation The 10 per cent that fail under medical management will require radical surgery because the ulcer has penetrated the wall of the duodenum with its floor formed by the head of the pancreas or the duodenohepatic ligament Of 47 primary duodenal ulcers for which Hinton operated in two years 42 were at the posterior wall of the duodenum Uncontrollable pain is the only real indication for surgery Other indications frequently considered are pyloric stenosis recurrent hemorrhage penetrating ulcers and lack of co operation in medical management

The only satisfactory procedure is subtotal resection with removal of the ulcer in toto Gastro enterostomy fails because the patient usually has not been referred for the ulcer but for the complication resulting from long existing ulcer—in most cases chronic pancreatitis Malplaced anastomosis is an important cause of failure in a high percentage of operations for gastric or duodenal ulcers If the anastomosis is placed 10–12 in and even farther from the ligament of Treitz a gastrojejunal ulcer is likely to develop

Indications for Operation in Cases of Peptic Ulcer from the Internist s Point of View Arthur L Bloomfield (Stanford Univ) states that pyloric obstruction is usually considered an indication for gastro enterostomy or pyloric resection While this is true in cases of vast dilation of the stomach associated with masses of scar tissue which throttle the pylorus there are border

(1) N w Y k St t J M d 45 91 95 F b 1 1945
( ) S g ry 17 69 696 M y 1945

Important complications warranting surgery include intractability of symptoms and failure of medical treatment perforation obstruction and hemorrhage Other factors include suspicion of neoplasm economic status forbidding regulation and upkeep of proper diet and care and associated gastric lesions

Gastric ulcer is a special problem because of the constant danger of carcinoma If there is reasonable justification to consider the lesion benign, use of a properly supervised *program for three weeks is an excellent diagnostic aid If the lesion fails to heal in three weeks or if* certain criteria suggest that the lesion may be malignant surgical exploration should be done immediately Recurrent ulceration at the site of a gastro enteric anastomosis usually requires further operation although some ulcers of this type respond to an adequately supervised medical regimen

Morlock believes that posterior gastro enterostomy has a definite place in surgical treatment It appears justified in selected cases in the presence of factors such as advanced age poor general condition low gastric acidity absence of gastritis a relatively inactive lesion single ulcer minimal neurogenic factors favorable personal habits and technical difficulties which would make gastric resection dangerous Subtotal resection with removal of two thirds to three fourths of the body of the *stomach is indicated if the patient is young or* middle aged and a good surgical risk if the lesion is active and there is history of subacute perforation and *repeated* hemorrhage if acidity is high if rather severe gastritis multiple ulcers or marked neurogenic factors are present if personal habits are poor if economic status is unfavorable and if technical difficulties are not too great *If* posterior gastro enterostomy is done without consideration in all cases of duodenal ulcer in which an exploratory *laparotomy is performed* a high incidence of unfavorable results must be expected

tion Operation should be done if bleeding continues despite transfusions Repeated persistent bleeding over a long time even without threat of exsanguination, calls for surgical treatment

Cancer develops so rarely in gastric ulcer that prophylactic excision is not usually indicated However, apparently benign ulcers which fail to heal promptly may be cancerous and should be removed by gastric re section Operation is also indicated in cases of intrac table symptoms even in absence of bleeding obstruction or perforation However, with better understanding of the complex of peptic ulcer and recognition of its psy chosomatic background operation will be done less often than before for indigestion without obstruction or hem orrhage it still has a place in refractory cases with in significant psychiatric symptoms Most of these patients probably should receive psychiatric treatment before surgery is instituted Either the psychic or the somatic component may predominate if the psychogenic factor is prominent operation should be considered only with great caution

[The author s view is one with which nearly all internists would agree The fact remains however that the view of most sur,eons and many pathologists is irreconcilable with that of the internist especially with reference to gastric ulcer One of my fair minded and well meaning surgical colleagues recently expressed the con viction that every gastric ulcer should be operated on It is true that many small ulcerating carcinomas masquerade as ulcer a fact which should never be lost sight of but on the other hand the large majority of lesions with symptoms and signs compatible with benignancy are benign lesions moreover frequently gastric lesions which for one reason or another we regarded as actually or probably malignant proved to be ben gn on microscop c examination

The role which spasm and edema play in pyloric obstruction which is frequently amenable to treatment can often be antic ipated by the duration and nature of the symptoms presented. This is especially true if the symptoms are not of long duration and pain is in the foreground. One refractory and otherwise objectively uncomplicated type of duodenal ulcer in a nervously stable individual is that which has slowly perforated into the pancreas Here an operation should be seriously considered if response to adequate treatment is incomplete —Ed]

Vagotomy in Therapy of Peptic Ulcer Vernon A. Weinstein Ralph Colp, Franklin Hollander and Ed

line cases in which inflammation of the mucous membrane with edema and spasm can often be treated without surgery For such cases the following routine is advocated

The stomach is emptied by washing with many liters of normal saline solution through a large (Ewald) tube The procedure must be thorough to reduce the dregs of retained material Washing is repeated each evening for several days *during which the patient is maintained with glucose saline solution and if necessary some form of protein digest administered parenterally* After two to four days the volume of residual secretion has usually decreased to less than 100 cc and fluids are passing through the pylorus Further proof of this may come from regurgitation of bile through the duodenum into gastric washings Small amounts of concentrated liquid nourishment are then given during the day and the stomach is thoroughly washed each night several hours after the *last feeding* to control stasis and permit the stomach to regain tone *while edema and spasm subside and the pyloric lumen widens Following this* the decision is made whether medical treatment should be continued or whether operation is necessary General clinical improvement roentgen examination of the stomach with umbrathor to show the irreducible degree of obstruction and stasis the patient s desire or ability to cooperate in a long time medical regimen his economic status and age and availability of surgical skill are factors in this decision *However if any doubt exists about success of medical therapy operation should be done*

Concerning the serious problem of hemorrhage from peptic ulcer most internists believe that a single even massive bleeding in a young person rarely kills and medical treatment is usually satisfactory Material for transfusions should be readily available in such a case However in older people severe bleeding especially if persistent with the possibility of erosion of a calcified vessel in *the base of the ulcer probably indicates opera*

will eventually prove to be effective The observations of Dragstedt and his associates (*Gastroenterology* 3 450 46?, December 1944) are encouraging in this respect They performed the operation in 11 patients by opening the left pleural cavity exposing the lower esophagus and isolating and dividing the vagus fibers before they pass through the diaphragm This was followed by striking relief of pain and ?0 per cent reduction of nocturnal gastric secretion It was recommended that patients with cicatric al pyloric stenosis have gastrojejunostomy in addition However sufficient time has not elapsed since operat on to permit of definitive appraisal

Krukenberg Tumors Roentgen and Gastro Enterologic Aspects of Secondary Ovarian Carcinoma Robert M Lowman and Samuel D Kushlan[4] (New Haven Conn) studied eight cases in five of which clearcut history of a gastro intestinal disturbance was obtained Ascites was recorded in four Five patients had bilateral ovarian involvement and three had involvement of the right ovary only Although diagnosis of the primary site was made in two cases ovarian involvement was not recognized at operation in the other six ovarian involvement was recognized first Generalized peritoneal carcinomatosis was present in six

Routine gastro intestinal study is important in every case of ovarian carcinoma Preoperatively such a survey should be made to determine the possibility of a primary tumor in the digestive tract When this has been omitted and even when a supposedly authentic primary carcinoma has been established at laparotomy postoperative study may reveal a primary tumor of the digestive tract Gastro intestinal symptoms occur in association with pelvic disease but it is unsafe to assume that this is a reflex mechanism without roentgen verification The importance of careful pelvic examination in any female patient with gastro intestinal symptoms was demonstrated in two cases During abdominal exploration for gastric cancer the possibility of ovarian metastases should be investigated Roentgen films of the gastro intestinal tract in either primary gastric or ovarian cancer should be studied for evidence of involvement of the small bowel In six of the eight cases generalized perito

(4) G t t l gy 4 305 3 Ap l 1945

ward E Jemerin[3] (Mount Sinai Hosp, New York City) studied six patients after partial vagotomy Two had had transthoracic vagotomies for gastrojejunal ulcer following subtotal gastrectomy In the third patient anterior subdiaphragmatic vagotomy a Stierlin circumcision vagotomy and jejunostomy had been performed for gastrojejunal ulceration following subtotal gastrectomy In the fourth patient subtotal gastrectomy and anterior subdiaphragmatic vagotomy had been done for duodenal ulcer In the fifth anterior subdiaphragmatic vagotomy alone had been done for functional gastric complaints and the sixth patient had had subdiaphragmatic vagotomy and gastro enterostomy for duodenal ulcer In the first two cases complete gastric vagotomy had been attempted but complete nerve severance had not been effected In all six cases vagotomy had been done as a last resort

The benefits of partial vagotomy in these patients are questionable The first patient was not improved and jejunal ulcer recurred The second patient died The third patient had recurrence of ulcer symptoms nine months after operation The fourth had recurrence of pain and vomiting 3½ months after operation but he has since been well partial gastrectomy alone might have produced the favorable outcome The fifth patient did not improve and developed difficulties in motility after operation In the last case operation was done too recently to justify conclusions

All six patients continued to have acid responses to insulin proving that vagotomy had been partial thus little reduction in the nervous phase of gastric secretion can be expected from this procedure This fact as well as the questionable influence of complete vagotomy on secretion has been demonstrated in experiments on dogs Thus neither partial nor complete gastric vagotomy can be recommended alone as a therapeutic procedure

[It is sincerely to be hoped that vagotomy in treatment of duodenal ulcer alone or in combination with other surgical procedure

(3) S rg Gyne & Ob t 79 9 305 S pt m

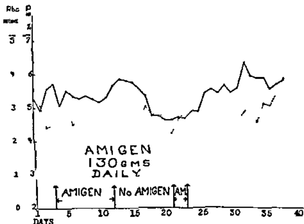


Fig 94 —D od al ul er 130 Gm mig n gi n th d th ugh tw lfth d y Se m p te n t 5 7 Gm f ll w d by f ll to 4 5 Gm. ft am g n d sconti ed t sfa tory se ga n w th u e f m g f m twenty first to twe ty th d d y in lus e.

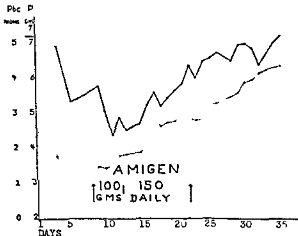


Fig 95 —G trie l er ste dy fall i erum p otein w th 100 Gm amigen d ily te dy se f ll wing inc se f daily mou t f migen to 150 Gm.

neal carcinomatosis was found at operation or autopsy Abnormal small intestinal patterns and dynamics suggest such involvement and may be a valuable contribution of the preoperative gastro intestinal examination Roentgen changes of peritoneal carcinomatosis consist of alteration of the mucosal pattern with coarsening irregularity and sometimes complete obliteration of normal folds of the small intestine The loops of small intestine are arranged in an atypical pattern The irregular bowel contours may show multiple serrations Contracted segments alternate irregularly with areas of dilatation, and many of these areas show prominent plicae and marked feathering of the margins Motility and tonicity of the bowel are frequently reduced some cases show extreme irritability abnormal segmentation and hypermotility

Effect of Oral Administration of 'Amino Acids' on Hypoproteinemia Resulting from Bleeding Peptic Ulcer Jerome S Levy[5] (Univ of Arkansas) states that the main factors influencing mortality from a bleeding point in the upper gastro-intestinal tract are patient's age severity of hemorrhage and presence of complicating diseases although the greatest probable factor is the kind of lesion i e presence or absence of a large open "pipestem artery The rationale of early feeding lies in supplying the tissues with exogenous protein However early feedings may start further bleeding unless the material given is predigested A mixture of amino acids would seem to contain agents necessary to correct hypoproteinemia resulting from hemorrhage and to provide an excellent buffer for gastric acidity Sufficient calories must be supplied also Levy therefore investigated the effects of a solution of amigen in 11 patients with bleeding from the upper gastro intestinal tract Amigen is the enzymatic hydrolysate of a pure casein and contains all essential amino acids Six other patients with similar bleeding were used as controls Both groups were given

(5) Gastroenterology 4 375 387 May 194

in ulcer patients with poor tolerance to ordinary pasteurized milk

Some of the results are shown in Figure 96 Averages of free acid values were lower after ingestion of enzyme treated milk than after ingestion of ordinary milk Average combined acidity was definitely higher with

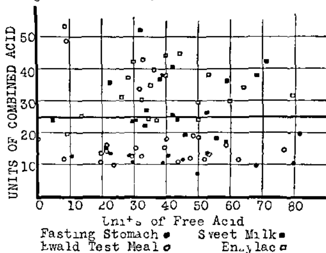


FIG 96—C mpa g m t f f e d w th am u t f mb ed d 5 p t ts u f st g t m h d ft Ewald t t m l sw t m lk d n yl

enzyme treated milk which also caused lower free acidity in 28 per cent of cases and greater combined acidity in 40 per cent In 70 per cent of cases the curds of the enzyme treated milk were smaller softer more friable and tended to float on the surface of the aspirated gastric juice Intimate mixing of enzyme treated milk with the gastric juice was shown by the milky appearance of aspirated gastric contents Most patients with intolerance to ordinary milk took the enzyme treated milk without discomfort The many symptoms of milk intolerance began to disappear in a few days and the patients complained less and were more energetic Frequently

the same diet and except for the amigen received equivalent daily nitrogen intake

Amigen was well tolerated Sufficient calories were given mainly in the form of glucose In the controls serum protein returned to normal in an average of 19 5 days In the 11 patients receiving amigen and glucose serum protein showed a prompt and steady rise reaching normal or near normal in 10–12 days This was particularly noticeable since the general nutritional condition of the patients who received amigen was far below that of the controls

The oral use of a mixture of amino acids in treatment of peptic ulcer especially with massive hemorrhage, is therefore especially advantageous Daily administration of amino acids in amounts totaling 3–3 5 Gm per kg has proved more satisfactory especially in presence of a poor nutritional state than the usual protein intake of 1 Gm per kg per day

Enzyme Treated Milk in Dietary Management of Patients with Peptic Ulcer F Steigmann and M L Blatt[6] (Cook County Hosp) report on a milk perfected jointly by the American Seal Kap Corporation and Armour Laboratories which is marketed as 'soft curd milk produced by the enzylac process or as enzylac It is prepared by addition of a pancreatic proteolytic enzyme to fresh market milk before pasteurization It has the taste appearance and mineral and vitamin contents of ordinary milk but becomes when acted on by gastric juice a soft friable curd of low tension rapidly digested and expelled from the stomach

Experiments were made to determine the comparative efficacy of enzyme treated milk and ordinary milk as acid modifiers and to compare their curd formation by measuring the size and amounts of curds left in the stomach one hour after ingestion of 200 cc of enzyme treated milk and of ordinary milk The subjective and objective effects of enzyme treated milk were observed

(6) Am J Dig t Dis 11 76–79 September 1944

General improvement of tabetic symptoms and diminution of gastric crisis and lightning pains occurred in all cases after injection The injections were spaced at monthly intervals or longer depending on frequency of attacks of pain Some patients required only one treatment for complete relief others needed as many as six injections Oral or subcutaneous administration of thiamine hydrochloride was of no avail

Gastric Carcinoma Observations on Peptic Ulceration and Healing Walter Lincoln Palmer and Eleanor M Humphreys[8] (Univ of Chicago) report four cases which illustrate the role of peptic digestion in ulceration in pre existent carcinoma and clinical and pathologic degrees of healing in these lesions under certain conditions Definite clinical evidence of pre existing benign



FIG 97 —D sap p f lce t d tre tm t persiste ce f filt t n f adj t port ns f g t w ll

ulcer was not present in any case In all duration and history were compatible with primary ulcerating neoplasm and there was gastroscopic evidence of neoplastic infiltration They are considered therefore as cases of gastric carcinoma with secondary peptic ulceration In all four cases benign ulcer was simulated in some respects but there were diagnostic signs of carcinoma Thus in the first two cases the lesions showed complete

(8) G t oe t rol gy 3 257 74 O t be 1944

enzyme treated milk gave relief when other modified milks soft curd or malted milk, did not

Enzyme treated milk, therefore should be considered not only a milk substitute in the dietary regimen of ulcer patients but also the ideal milk for most of these patients Both secretory and motor phases of gastric activity in peptic ulcer are benefited by it

[Milk or its products is the keystone in the dietetic arch of ulcer therapy In my experience the objection to milk in most ulcer patients is without foundation Except in that small percentage who are actually allergic to it milk and its modifications with appropriate antacids can usually be taken Sometimes simple modifications such as boiling or flavoring with cinnamon stick vanilla cocoa weak tea or Vichy water make it more acceptable Some years ago Blankenship and Oatway recommended adding strained orange juice to the milk cream mixture to make it more digestible Borden has recently introduced Mull Soy also effective as a temporary milk substitute It is to be hoped that enzyme treated milk will also prove a valuable addition among substitutes for the orthodox milk or milk cream mixture —Ed]

Intraspinal Thiamine Hydrochloride in Treatment of Gastric Crisis or Lightning Pains in Tabes Dorsalis Benjamin H Kesert and Maurice O Grossman[7] (Veterans Admin Facility Hines Ill) report eight cases with either tabetic crisis or lightning pains in which intraspinal injection of thiamine hydrochloride was beneficial This method offers the greatest relief from pain It may be necessary to give a patient three or four injections a year Optimal dose is 50 mg but as much as 100 mg may be given at one time Following injection, the patient may complain of a feeling of warmth in the extremities and exacerbation of pain for about 24 hours, then the patient may be symptom free for several weeks or months or even longer The method is harmless and obviates further use of morphine or surgical measures

TECHNIC —With the patient on his side the needle is inserted in the interspace between the third and the fourth lumbar vertebra When clear cerebrospinal fluid starts to flow the thiamine hydrochloride in the syringe is diluted with cerebrospinal fluid and injected into the subarachnoid space The needle is withdrawn and the patient placed on his back He is kept in bed for 12 hours

(7) J Nerv & Ment Dis 101 372 377 April, 1945

destruction of an area of muscle corresponding in size roughly to the floor of the ulcer and presence of a large area of dense fibrous and granulation tissues covered by a necrotic layer These are considered classic characteristics of a benign ulcer but Mallory suggests that they be considered histologic evidence of peptic ulceration If one accepts the concept of peptic ulceration in gastric cancer the process might then produce sometimes all the features characteristic of benign ulcer including fusion of muscular layers Evidence obtained in the first two cases suggests that this is true

The process of healing in peptic ulceration in benign ulcer is apparently similar to that in peptic ulceration in tumor tissue as shown by marked decrease in size of the roentgenologic crater seen in one case (Fig 97) The manner in which the scar may be infiltrated by neoplasm and covered with a neoplastic epithelium or with a layer of normal epithelial cells (Fig 98) is rather surprising These phenomena indicate a mechanism by which the clinical symptoms roentgen evidence and gastroscopic evidence of a gastric neoplasm may disappear under treatment as reported by Eusterman

[In some of the authors cases the slides shown depict ulceration incident to extensive gastric carcinoma in view of the associated telltale filling defect Others have reported healing of small ulcerating carcinomas presenting niches only and which were indistinguishable from benign ulcer Nevertheless this contribution delineates the factors involved in actual or apparent healing of the ulcerative process Conversely I have seen persistence of small niche or fleck defects due to pitlike depressions left by the healed ulcer the benign nature of which was histologically proved Such a phenomenon has also been reported in a few instances by others —Ed.]

BILIARY TRACT AND PANCREATIC SYSTEM

Eck Fistula Liver Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron C H Whipple F S Robscheit Robbins and W B Hawkins[9] (Univ of Rochester) studied the path

(9) J Exp Med 81 171 191 February 1945

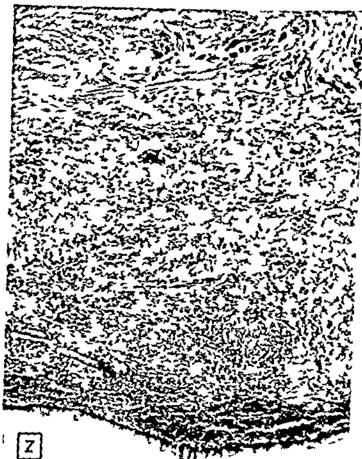


FIG 98 —Same ca p d g Ile l d m t u ul er bows ep th l ed surface c n t ng of r w of t ll lumnar mu us ell t g on th n zone of ve y va ul r c nn t e t e B neath w de band dens l infil trated w th signet r g c n er c lls a d leuk vt *mainly mono nc ear c* eosinophil S m la s gnet r g c ll d n st of m re ompact darkly stained can e cells nfilt ate p p mu lar t r cognizable mus ul r mucosae in th s part F nd gs clearly ind te be l ng in ul rat v neo plasm f esh g anul t on t ue overly ng the ncer a d o e d by non neoplasti p thel um P rf ct pol r z d lls f m ng th s simpl ep thel l layer are identi l w th th se found on a f of n m l g t mu o a

destruction of an area of muscle corresponding in size roughly to the floor of the ulcer and presence of a large area of dense fibrous and granulation tissues covered by a necrotic layer These are considered classic characteristics of a benign ulcer but Mallory suggests that they be considered histologic evidence of peptic ulceration If one accepts the concept of peptic ulceration in gastric cancer the process might then produce sometimes all the features characteristic of benign ulcer including fusion of muscular layers Evidence obtained in the first two cases suggests that this is true

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(9) J E p Med 81 171191 F bru ry 194

ology and physiology of the liver of dogs with Eck fistulas These animals can remain in an apparent state of health for many years The fistula permits portal blood to flow freely into the vena cava and excludes portal blood from the liver the blood supply to the liver is arterial and probably only 25-35 per cent of normal *The liver shows slight gross and histologic changes*

Experiments showed that chloroform is tolerated by the Eck fistula dog which may take twice the lethal dose for a control dog without evidence of significant liver injury Acacia given by vein is deposited in the Eck fistula liver and further impairs its functional capacity to contribute to hemoglobin production The stress of anemia shows that the anemic Eck fistula animal cannot utilize *standard diet factors and iron as efficiently as the anemic* control without an Eck fistula The output of new hemoglobin in some instances may drop to one fourth of normal When hypoproteinemia alone or combined with anemia is produced in the Eck fistula dog there is at times very low production of plasma proteins, even a drop to one tenth of normal

This interrelation of liver abnormality liver dysfunction and lessened plasma protein and hemoglobin production is significant It is generally accepted that the liver is concerned with production of several plasma proteins, such as fibrinogen prothrombin and albumin These experiments indicate that it is concerned directly or indirectly with production of new hemoglobin The authors believe that the liver contributes to production of hemoglobin by means of the mobile plasma proteins which *to a large extent derive from the liver*

Tests of Liver Function James F Weir[1] discusses liver function tests commonly used at Mayo Clinic during the past few years

The van den Bergh test is used to determine type and quantity of serum bilirubin it can also be applied to duodenal contents and urine The technic of Sepulveda

(1) M Clin North Ame i a 9 973 981 July 1945

and Osterberg permits quantitative determination separately of indirect and direct reacting bilirubin in the serum in any given case In health the bilirubin level is less than 0 6 mg per 100 cc serum and the bilirubin reacts indirectly with Ehrlich s diazo reagent In pathologic states such as pernicious anemia congenital hemolytic icterus other hemolytic conditions and familial hyperbilirubinemia the reaction is characteristically indirect and serum concentration usually is variably increased In many cases of cirrhosis and metastatic tumors of and other pathologic conditions of the liver without evident jaundice the reaction may be indirect This type of reaction does not exclude any of these pathologic processes Pigmentation such as that due to carotene and atabrine must be distinguished from icterus When pigmentation is due to these substances bilirubin concentration is normal and the reaction indirect A direct reaction is always pathologic and is usually found in obstructive and hepatogenous jaundice latent jaundice after biliary colic acute cholecystitis metastatic tumors of the liver and many cases of chronic and even acute hepatitis In the presence of a hemolytic process a direct reaction indicates associated hepatic or biliary disorder Biphasic or delayed direct reactions are relatively unimportant clinically The quantitative determination shows the degree of retention of bilirubin and its fluctuations Estimations every few days may be necessary to determine whether jaundice is stationary increasing or decreasing In obstructive jaundice due to stone in the common bile duct average value for serum bilirubin is 10–15 mg per 100 cc In neoplastic obstruction of the common bile duct average values are higher i e 20–30 mg Fluctuations seldom occur and jaundice is persistent In parenchymatous liver disease degree of icterus is variable from very mild degrees of bilirubinemia to as much as 70–100 mg In obstructive jaundice similarly high concentrations indicate associated hepatic degeneration

The icterus index is a simple and approximate method for following the degree and variations of bilirubinemia in any case of icterus

Dye excretion tests are used to determine liver function Bromsulfalein 5 mg per kg body weight is injected a specimen of blood is removed in one hour and the amount of dye remaining in the blood is determined with a blood colorimeter Normally little remains 40 per cent or more indicates a high degree of retention The test is one of the best in cases in which jaundice is not present Jaundice is a contraindication to its use The test is valuable in enlargement of liver and spleen suspected metastatic tumor or abscess ascites and toxic hepatitis such as may occur in cases of exophthalmic goiter toxemias of pregnancy many infections and poisoning with various therapeutic and industrial chemicals

The hippuric acid test depends on ability of the liver to furnish glycine to permit synthesis of hippuric acid from benzoic acid and is supposedly a test of the detoxicating function of the liver It can be used only if the kidneys are healthy Urinary hippuric acid excretion is determined gravimetrically After administration of 6 Gm sodium benzoate at least 2 5–3 Gm as hippuric acid should appear in the urine in four hours Less than 1 5 Gm indicates impairment of liver function

The galactose tolerance test is a sugar tolerance test used to determine deviations of normal function of the liver to metabolize carbohydrates Galactose is chiefly utilized by the liver and for the test it may be given orally or intravenously When given intravenously, the test is called the galactose clearance test Diabetes mellitus is a contraindication If galactose is given orally 40 Gm in 500 cc water is administered and urine collected over a five hour period and examined for sugar Normally less than 3 Gm sugar should be excreted Excretion of over 5 Gm indicates severe hepatic damage In acute hepatitis positive tests may be obtained early *The test has been mildly positive in 50 per cent*

of cases of malignant obstruction and in 25 per cent of cases of obstruction due to stone or cicatricial stricture Normal results do not exclude the possibility of parenchymatous origin of jaundice

Prothrombin time should be determined in all cases of jaundice particularly if the disease is surgical in which case it should be determined before and after operation Quick s method modified by Magath is used Normal values are 18–20 seconds Elevation may be due to deficient intake absorption or utilization of vitamin K Deficiency of absorption is common in the acholia of jaundice and also occurs in intestinal disorders such as sprue Deficiency of utilization is found chiefly in parenchymatous di ease of the liver Degree of failure is an indication of hepatic insufficiency Vitamin K should be given in all cases of jaundice regardless of prothrombin time particularly if operation is to be performed administration is continued postoperatively

Another test is determination of distribution of urobilinogen in feces and urine modified by Watson Normally much of the bilirubin of bile entering the intestine is changed to urobilinogen Much of this is absorbed into the blood stream passes to the liver and is reconverted to bilirubin Normally 30–200 mg urobilinogen is excreted in the feces during 24 hours Small amounts appear in the urine Persistent absence of urobilinogen from feces and urine indicates complete obstruction of biliary passages most frequently seen in malignant tumors and occasionally due to a stone impacted in the common bile duct or complete cicatricial stricture of the bile ducts Marked increase up to 3 600 mg in 24 hours is found in various hemolytic processes

Other tests include determination of serum protein content fats in plasma and blood urea and serologic tests based on alterations of blood proteins

Weir is convinced that diagnosis and management of diseases of the biliary tract and liver are largely based on clinical grounds and that the various tests have lim

ited value They are somewhat helpful in following the clinical course of hepatic disease, in determining risk of surgical procedures in directing pre and postoperative treatment and medical therapy and in evaluating prog nosis Proper interpretation of the tests is obviously of first importance

Clinical Value of Functional Tests of Liver J Gar rott Allen (Univ of Chicago) recommends use of sev eral different types of tests in the study of hepatic dis ease Not all tests are equally effective and no single test reflects the functional state of the entire liver The name liver function test should be abandoned, therefore and the name of the specific test used

Tests which are so sensitive as to be positive when other evidence of liver disease is lacking are not helpful to the clinician Tests which indicate greater hepatic damage than the clinical course warrants are the floccu lation tests such as the cephalin cholesterol flocculation colloidal gold and hippuric acid excretion tests, while values for plasma prothrombin galactose tolerance plasma proteins bromsulfalein excretion, cholesterol and cholesterol esters are frequently normal in advanced liver disease In the patient with liver disease but with out jaundice the bromsulfalein excretion test prothrom bin response to vitamin K and serum albumin globulin ratio offer simple and efficient means of detecting signifi cant liver damage In the icteric patient when diagnosis lies between obstructive and intrahepatic jaundice the character of prothrombin response to vitamin K may establish diagnosis when all other methods short of op eration have failed the urobilinogen test described by Watson *et al* also aids here The prothrombin test re quires that significant prothrombin reduction be ob tained that the patient be eating reasonably well and that he be afebrile With these criteria and a sensitive prothrombin determination differentiation of obstruc tive and intrahepatic jaundice can be made with a high degree of accuracy

(2) Gastroenterology 3 490 505 December 1944

Cephalin Cholesterol Flocculation Test Leo J Wade and Ellen Ehrenfest Richman[3] (Washington Univ) investigated this test which aids in early diagnosis of cirrhosis and indicates the change in hepatic function produced by therapy Their analysis covers 500 tests done on serums of patients whose diagnoses were established mostly at autopsy or operation or were supported by unmistakable clinical evidence

Serums of 178 patients with known diffuse parenchymatous liver disease produced flocculation of the cephalin cholesterol emulsion in 173 instances Only five serums gave negative reactions Two of these occurred in presence of cirrhosis which anatomically was early but definite the third in presence of carcinoma of the liver the fourth in presence of diffuse atrophy of the liver and the fifth in a case of late catarrhal jaundice Discrete lesions of the liver involving only a small part of the parenchyma were associated with significant flocculation in 53 3 per cent of cases There was *no correlation* between *presence duration or severity* of jaundice in these cases and presence or absence of flocculation Of 180 cases in which reasonable suspicion of hepatic dysfunction existed definite flocculation occurred in 67 Cholecystitis and cholelithiasis were responsible for 21 of these reactions chronic passive congestion for 24 and chronic alcoholism for 8 No correlation could be established between duration of cholecystitis and cholelithiasis and presence or absence of flocculation Possibility of detecting early cirrhosis among patients with alcoholism was carefully studied although 20 per cent of such patients had significant flocculation none had returned with clinical cirrhosis even though two to three years had lapsed in some instances

False positive reactions occur during infections in presence of allergic disease or during the puerperium. Negative reactions are found in presence of minimal lesions but they usually indicate absence of hepatic dys

(3) J L b & Cl n Med 30 613 J n ry 1945

function No particular value can be ascribed to the test in differentiation of obstructive from nonobstructive jaundice Quantitative changes in globulin have no ap parent role in determining occurrence of positive reac tions Maximal value of the cephalin cholesterol floccu *lation test is apparent in acute hepatitis catarrhal* jaundice cirrhosis or any other diffuse parenchymatous disease of the liver a negative reaction does not, how ever exclude these lesions

Cephalin Cholesterol Flocculation Reaction As Test of Hepatic Function was used by Archibald Dick[4] (Royal Northern Infirm Inverness)

METHOD —Hanger s method was used to obtain the brown powdery cephalin by extraction from sheep brains A stock solution was prepared by adding 300 mg cholesterol and 100 mg cephalin to 8 cc ether This preparation was kept at 0–5 C To prepare the emulsion 35 cc distilled water was heated to 65–70 C and 1 cc stock solution was slowly added with frequent stirring The mul sion was heated to boiling point and allowed to simmer until volume was reduced to 0 cc This was cooled to room temperature and 1 cc. emulsion was added to a centrifuge tube containing 0 2 cc serum and 4 cc freshly prepared 0 85 per cent sodium chloride The tube was then stoppered shaken and left at room temperature for 24 hours If flocculation was then present it was designated zero to 4 plus. The serum must be used immediately or kept in an ice box not more than six hours Final reading should be made in 24 hours, as normal serum may cause positive flo culation in 48 hours

Dick applied the test to healthy blood donors patients with various systemic diseases without clinical evidence of hepatic disease and patients with hepatic or biliary disease Of the 100 normal persons only 1 had a 4 plus reaction and this person was found to have hepatic dis ease Positive reactions were seen in 13 of 164 patients with systemic disorders including pernicious anemia malaria, lung cancer pleurisy with effusion diabetic coma gastric cancer nephritis and hemolytic anemia due to sulfonamide therapy rheumatoid arthritis iron defi ciency anemia asthma and diaphragmatic pleurisy Three patients had negative reactions when discharged after treatment of their primary condition however

(4) B r M J 1 18 185 Feb 10 194

two with rheumatoid arthritis had positive reactions on several occasions even though careful investigation revealed no hepatic disease

Most patients in the third group had hepatitis (38) or biliary tract obstruction (15) Of 26 with acute infective hepatitis all had positive reactions with all but seven markedly positive The test is therefore sensitive in detection of parenchymatous liver disease Furthermore the reactions parallel clinical severity of the disease thus being of value in prognosis Of 12 patients recovered from jaundice 10 had negative reactions and 2 who had had fairly severe attacks of hepatitis positive reactions Only one patient with obstructive jaundice had a positive reaction diagnosis was based solely on clinical examination There was long standing jaundice with undoubted damage to the liver cells and finally death Of nine patients with a fairly certain diagnosis of cirrhosis of the liver three had positive reactions Three patients with secondary cancer of the liver had negative reactions Of two other cancer patients one had a 2 plus and the other a negative reaction both had evidence of hepatic inefficiency Of 12 patients in whom jaundice developed during arsenical treatment of syphilis only 7 had positive reactions five of which were strongly positive Thus the test is useless in early detection of liver damage in arsenical jaundice

Mechanism of Positive Cephalin Cholesterol Flocculation Reaction in Hepatitis is discussed by David B Moore *Paul S Pierson Franklin M Hanger and Dan* H Moore[5] (Columbia Univ) Previous investigation showed that the gamma globulin fraction of the serum was the sole component giving a positive flocculation and that there was no difference in the flocculating power of the gamma globulin fraction obtained electrophoretically from normal serum giving a negative reaction and that obtained from hepatitis serum giving a strongly positive reaction It was inferred that negative floccula

(5) J Clin I e t g t 4 9 95 M y 1945

tion obtained with normal serum was due to the inhibiting action by some other component of the serum. Complete inhibition of the reaction was not obtained with the albumin fraction although inhibition of the colloidal gold reaction which showed many points of similarity, was obtained with electrophoretically separated albumin. The authors therefore decided to investigate these phenomena further. Serums were taken from normal subjects giving a negative flocculation reaction and from two patients with obvious liver disease and 4 plus reactions. The first patient had acute fulminating postarsphenamine hepatitis and the second catarrhal jaundice. Cephalin flocculation tests were performed on separated serum fractions using diminishing amounts of the globulin fraction alone and also after addition of various albumin fractions. Protein preparations were mixed with merthiolated saline and the standard cephalin cholesterol emulsion.

As the gamma globulin fractions were progressively diluted flocculation diminished and was usually abolished at a concentration between 0.22 and 0.11 mg. of gamma globulin in 5.2 ml. of diluent. No significant differences in flocculating properties were noted between the gamma globulin fraction from hepatitis serums and a similar fraction from normal serum. The albumin fraction never under similar conditions, gave a positive flocculation. Protein fractions were separated electrophoretically in a phosphate buffer at pH 7.4 near the iso-electric range of gamma globulin. The gamma globulin fraction obtained at pH 8.5 using a barbital buffer failed to show flocculating properties even after dialyzing to restore pH to 7.4.

When albumin was added to gamma globulin, considerable inhibition of flocculating properties of the gamma globulin was obtained when the albumin fraction was from normal sources. An equal amount of albumin fraction from the two patients with hepatitis showed distinctly less inhibiting power.

The authors advance the hypothesis that the gamma globulin component of normal serum does not produce flocculation because of an inhibitory action exerted by substances in the electrophoretically separated albumin fraction In disease, a positive flocculation is obtained with a serum owing to any of the following alterations (1) increase of gamma globulin in such quantity that there is insufficiency of normal components of the serum albumin fraction to inhibit the reaction (2) diminution of serum albumin fraction below initial levels necessary to inhibit the reaction and (3) diminution in floccula tion inhibiting properties of the albumin fraction

Fasting Blood Sample Procedure in Differential Diagnosis and Management of Hepatic Disease David Schwimmer S D Klotz I J Drekter and Thomas H. McGavack[6] (New York Med College) discuss a composite test which is a combination of simultaneous determinations of the icteric index van den Bergh reaction cephalin cholesterol flocculation and levels of phosphatase total cholesterol cholesterol esters total proteins albumin and globulin Modifications in the various tests made them simpler and more economical but without reducing accuracy The composite test was used 1 400 times in 750 patients—47 3 per cent with intrahepatic and 12 7 per cent extrahepatic conditions 6 1 per cent hemolytic processes and 33 9 per cent miscellaneous diseases Diagnoses were confirmed by clinical findings and ourse x ray examinations peritoneoscopy biopsy, operation and autopsy

The cholesterol ester/total ratio and the cephalin flocculation reaction were the most sensitive indexes of intrahepatic disturbance the percentage of esters being the more reliable of the two The composite test used as a unit compared favorably with other liver function tests many of which were frequently performed in parallel It was more reliable for differential diagnosis and for indicating progress of disease than were the 2 mg

(6) Am J D g t Di 1 1 15 Ja ry 1945

bromsulfalein, oral galactose tolerance and oral hippuric acid tests and about equal to these in estimating hepatic reserve Graphs were made on the basis of the cases to illustrate findings to be expected in a particular hepatic disturbance (Figs 99–102) Figure 99 represents a case of hepato cellular jaundice with recovery Initially, all values tend to rise as a result of intrahepatic obstruction As cellular damage progresses cephalin flocculation be

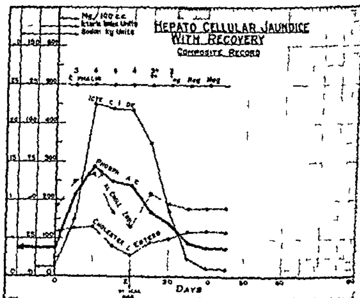


FIG 99

comes markedly positive and percentage of esterified cholesterol falls When damage progresses a striking fall in percentage of esters occurs followed shortly by perceptible reduction of total cholesterol Simultaneously the phosphatase value falls This trend continues until the critical phase—three weeks on the average in these cases—when signs of improvement occur Icteric index drops rapidly, and phosphatase level falls gradually Total cholesterol and ester percentages rise somewhat

abruptly with the former likely to reach temporary levels slightly above normal The intensity of cephalin flocculation during this period gradually diminishes Serum proteins are not characteristically altered at any stage In the type of case shown in Figure 99 recovery may be expected within five or six weeks

In cases of hepatocellular jaundice without improvement (Fig 100) serial determinations demonstrate pro

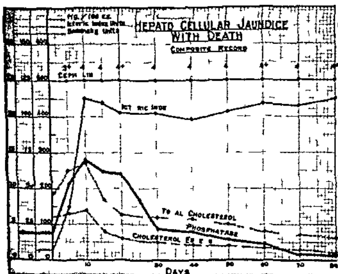


Fig 100

gressive irreversible reduction in both total and esterified cholesterol to significantly low levels with constantly diminishing ester/total ratio As hepatic damage increases phosphatase falls at first rapidly toward normal then gradually to subnormal levels The cephalin reaction usually remains 4 plus Serum proteins predominantly normal during early phases show a gradual drop with hypo albuminemia hyperglobulinemia and tendency to reversal of the albumin/globulin ratio The

period from onset to death may vary from a few weeks to several months, and speed with which results of the tests change is prognostic of the rapidity with which death ensues

When the common duct is blocked by stone serial examinations show uniform proportionate rise in icteric index phosphatase total cholesterol and cholesterol esters when obstruction takes place (Fig 101) The high

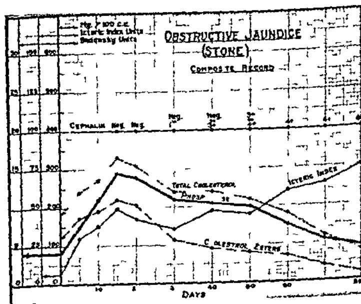


Fig 101

levels are maintained as obstruction persists and they fluctuate with the degree of obstruction Percentage of cholesterol esters is well maintained for two to three weeks and the cephalin reaction is either negative or only minimally positive for even longer In comparison with parenchymatous jaundice calculous obstruction generally has a lower icteric index The phosphatase level though perhaps lower than in early hepatocellular jaundice stays elevated whereas in hepatocellular jaundice

it invariably falls as the disease continues and may reach subnormal levels If the block is relieved by operation all values return to normal rather quickly If obstruction is not relieved severe liver damage secondary to pressure develops with a downhill course Strictures and inflammatory lesions blocking the common duct usually produce a similar picture

Neoplastic obstruction of the flow of bile into the

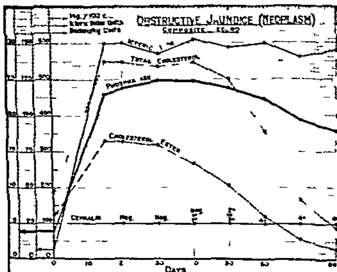


Fig 10

duodenum presents a unique picture in the composite test (Fig 102) There is progressive concomitant rise of values for icteric index phosphatase total cholesterol and cholesterol esters The cephalin reaction remains negative and percentage of esters is maintained at a high level for a fairly long period In contrast to benign obstruction and parenchymatous jaundice however unprecedentedly high values are seen with this syndrome icteric index ranged between 100 and 190 units in these

cases, total cholesterol between 500 and 1,200 mg per cent and phosphatase between 18 and 35 Bodansky units These elevations may persist for a long time When *obstruction has been present for long the first indication* of liver damage is usually reduction in percentage of cholesterol esters Then the cephalin reaction slowly becomes positive concentration of total cholesterol drops and finally the value for phosphatase begins to fall All this occurs with persistently deep icterus with a high index With intermittent obstruction and jaundice, test values vary but continue to reflect the balance between parenchymal and obstructive phases of the process Total and fractional protein levels are only moderately affected in the early *stages of neoplastic obstruction These* values become abnormal when secondary parenchymal changes have occurred Hypo albuminemia and reversal of albu min/globulin ratio follow reduction in percentage of cholesterol esters and increase in cephalin flocculation

[The foregoing contributions dealing with functional tests of the liver have been culled from numerous others appearing in the cur rent literature Such tests are an aid to not the sine qua non of diagnosis We must continue to place our chief reliance on time honored methods i.e case history physical examination and when ever necessary hospital observation It is essential to be familiar with one reliable set of tests rather than to have a casual acquaint ance with many A pathologic reaction is significant but a nega tive one no more excludes organic changes than a normal chole cystographic response excludes noncalculous cholecystitis or even the presence of gallstones And then the frequent association of parenchymatous hepatic disorders with surgical lesions of the gall *bladder and biliary tract can send us into a diagnostic* tail pin if we rely too much on laboratory methods —Ed]

Value of Liver Puncture in Diagnosis of Various Dis eases of Liver I Hatieganu T Sparchez P Radu and I Macavei[7] used liver puncture in 45 cases, *employing* a 2 cc glass syringe and long thin needle Puncture should be done in the morning one half hour after the fasting patient has been given 15 drops of pantopon By applying slight suction a punctate is obtained which is rich in liver tissue and contains only a little blood The cytologic preparation of the punctate on the microscopic

(7) Wien klin. Wchnschr 56 127 Jan. 15 1943

slide is called a hepatogram In 11 cases of tumor of the liver puncture proved valuable in obtaining biopsy material Diagnosis of carcinoma in the initial stage was made from the hepatogram which was characterized by lack of uniformity of cells associated with abnormal increase and irregular arrangement The puncture is valuable in distinguishing liver carcinoma from sarcoma particularly melanosarcoma Deep dark pigment in the form of egg shaped granules fills almost the entire cell protoplasm and is localized around the nucleus Cellular alterations may likewise be demonstrated on the hepatogram in grave cases of hepatic parenchymatitis and particularly in icterus of the cholangitic type

Puncture has practical value in cases of pigmentary cirrhosis in which medium sized single or multiple brown granules are found within or outside the protoplasm even in atypical cases without bronzed skin Immature blood elements are demonstrable in the hepatogram in leukemia the premyelocytes and myelocytes may predominate and there may be some myeloblasts and basophilic erythroblasts The microscopic picture of a hepatogram in acute leukemia resembles that of the myelogram so that liver puncture is unnecessary in such cases although it is valuable in aleukemic and erythroblastic leukemia In pernicious anemia the megaloplastic function of the liver is demonstrated in the hepatogram Liver puncture may reveal the causative agent in cases with a slow septic course and may clarify the bacteriologic diagnosis of the condition

Cirrhosis of Liver Correlation of Composite Liver Function Studies with Liver Biopsy Frederick W Hoffbauer Gerald T Evans and Cecil J Watson[8] (Univ of Minnesota) report cases of liver disease which involved either cirrhosis or conditions in which diagnosis of cirrhosis had to be considered and which illustrate many of the difficulties of differential diagnosis A composite liver function study is helpful Figure 103 shows results

(8) M Cl N th Am 9 363 388 M h 1945

of such a study recorded on a standard form which per mits ready comparison of the disturbance of individual functions with the degree of jaundice and biliary ob-struction For the nonjaundiced patient the following

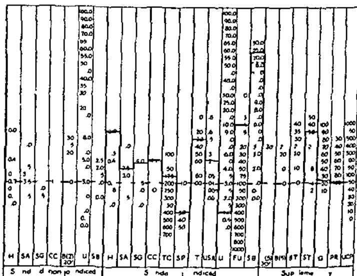


FIG 103 —C s 1 Li er f nct on tudy A gust 25 to S pt mber 10 f lu s e W k ng d ag os rho b l ary t ct c c n ma F l d g o s cirrh s Key to Col mn Des g t ons *H* h pp c c d in grams, o e h r uri e specimen (1 77 Gm s d m b t t a e o ly) *SA* erum l b min in gram p r 100 c *SG* ser m gl bul n in grams per 100 cc *CC* ceph l n h l te 1 0 to 4+ *B(2)* b m ulfale n, mg pe kg pe e t retai ed *B(5)* b om ulf l 5 m p kg l per e t ret d, *SB* total serum b l rub n n m ll grams p r 100 c (l we b ke l [whe p e ent] equals 1 mi f ead g upp b oke l ne 15 m nute d g) *UU* urin u ob l g n m ll gr m per 24 h *FU* feces u ob l noge in mill g m per 24 h urs *TC* t t l se um b lest l n m ll gr ms pe 100 c *PT* proth omb n p c t of norm l *BT* b l rut n t l ra per c t reta d 4 ho rs ft 1 mg p kg t a n u ly *ST* ste b l t leranc m ll grams (as b linoge) app r g n 24 h r uri after 50 mg *G mill g ams of galactose in bl d 75 m n tes fter* 0 5 Gm. per kg tra n usly *PR* p t po f p oth t towa d normal afte 1 mg 2 m th 1 l 4 naphthoqu no e int a e u ly *SP* rum ph s phatase n unit *UCP* ur p porphyrin n g mm s per 24 h rs *USR* uri e tool urobil og n r t o

procedures are included in composite study *quantitative* serum bilirubin and fractional serum protein determina tions hippuric acid synthesis and cephalin-cholesterol flocculation bromsulfalein excretion and quantitative

urine urobilinogen tests For the jaundiced patient the same group of tests except for bromsulfalein is used and in addition the serum cholesterol and alkaline phosphatase prothrombin time before and after vitamin K administration and feces urobilinogen are determined In the liver function chart the values above the midhorizontal line indicate in general a diminishing liver function while those below the line indicate either normal liver function or simple biliary obstruction without disturbance of function By connecting the various values plotted a profile of liver function for any given case is obtained Certain forms of cirrhosis or other liver disease as well as extrahepatic biliary obstruction exhibit fairly characteristic profiles however more experience is needed before strict differentiation is feasible on the basis of such studies eventually correlation of sufficient data of this type with histologic appearance of the liver may permit diagnostic deductions from graphs alone



FIG 104 —C e 4 Needl b psy f li e xt n e rrh with som n w b l d t d ke m es within hepat ds H mat xyl n s n

Specimens of liver were obtained with the biopsy needle in 70 cases of liver disease This method often permits accurate diagnosis when laboratory and clinical findings are inconclusive Fifty of the specimens were obtained at the bedside and 20 in the operating room under peritoneoscopic control The Vim Silverman needle was used In 15 additional cases attempts to secure specimens were unsuccessful A serious but nonfatal hemorrhage occurred in one case

Correlation of composite liver function with results of liver biopsy has given additional facts about the pathologic physiology of jaundice and liver disease Thus it has become increasingly apparent that cirrhosis of similar anatomic extent may exhibit strikingly different degrees and type of liver function impairment Diagnosis of obscure or uncommon liver disorders, e g , primary amyloidosis has been established by biopsy in cases in which results of composite liver function although abnormal, were not diagnostic

Hepatitis Due to Injection of Homologous Blood Products in Human Volunteers John R Neefe Joseph Stokes, Jr John G Reinhold and F D W Lukens[9] (Univ of Pennsylvania) using nine human volunteers for inoculation were able to confirm the fact that plasma or serum may contain a transmissible agent capable of producing hepatitis Of the five who received intravenous injections of a pooled mumps convalescent plasma four developed hepatitis with jaundice the fifth had mild hepatitis without jaundice Plasma from one of these men 23 days after inoculation was injected intravenously into two other men both developed mild hepatitis without jaundice The donor of this plasma developed jaundice 87 days after the plasma had been taken Subcutaneous inoculations of yellow fever vaccine in two men produced hepatitis, one with and one without jaundice Frequent liver function studies were required in all cases to detect presence of hepatitis In further experi

(9) J Clin Investigation 23 836 855 September 1944

ments one volunteer was reinoculated with the same material after recovery from the first attack and had not developed hepatitis during the 140 days so far elapsed The disease began 12–35 days after inoculation in six of the nine subjects This is in contrast to Cameron s findings who reported that in some cases onset was delayed as long as six months

Comparison with results reported in the literature shows that age of the subject as well as size of the group may influence incidence the younger the subjects and the smaller the group the higher the incidence of disease Bilirubinuria was among the first signs of hepatic disturbance sometimes appearing long before there was significant increase in concentration of total serum bilirubin In one case it was the only definite finding suggesting activity of the disease during the symptom free interval that immediately preceded the final stage of hepatitis with jaundice No single test was absolutely reliable tests for serum bilirubin concentration bilirubinemia cephalin flocculation bromsulfalein retention plasma vitamin A level and prothrombin activity appear to be most satisfactory

[It is ev dent that the m l tary medical personnel was plagued by frequent occurrence of three types of hepatitis namely infectious (epidem c) homologous serum and toxic hepat tis espec ally the first two Jaundice when present facil tated diagnos s and treatm nt Accumulated evid n e ha fa rly well established the fact that the hepatogenic or cterogenic factor probably a virus is a syringe transmitted one necessitat ng a change in p esent injection technic especially regarding sterili ation of syringes and needles Stokes and his associates in subsequent contribut ons have demonstrated the usefulness of gamma globul n from pooled human plasma in prevent on and attenuation of infectious hepatitis —Ed]

Constitutional Hepatic Dysfunction Mandred W Comfort and Robert M Hoyne[1] (Mayo Clinic) report 35 cases in patients aged 16–65 Jaundice had been noted since childhood in some cases and later in life in others In some the jaundice had appeared only a few weeks before admission Only 50 per cent knew that they had jaundice It was intermittent or chronic Familial tend

(1) G t nt l gy 3 155 16 S pt mb 1944

ency was definite in 20 cases was denied in 5 and could not be ascertained in the rest The jaundice was characteristically produced or aggravated by fatigue, nervousness worry premenstrual tension migraine, vertigo and intoxication and was much worse after constipation or dyspepsia

The essential pathologic condition was abnormal concentration of serum bilirubin giving the indirect van den Bergh reaction Values for serum bilirubin ranged up to 10 9 mg per 100 cc The van den Bergh reaction was indirect in 34 cases in the remaining case it was delayed *direct with great concentration The sole physical finding* in these cases was the slight icterus and elevation in concentration of bilirubin was the only positive laboratory sign

The condition may be acquired or congenital it is apparently not due to hemolytic biliary or hepatic disease and apparently does not cause symptoms The dysfunction may be due to an inborn deficiency of the hepatic cell Its recognition is important so that unfavorable prognosis and unnecessary surgical treatment may be avoided The condition is compatible with good health.

Occlusion of Hepatic Veins Mavis P Kelsey and Mandred W Comfort discuss 20 cases 4 of their own and 16 from the literature in 16 of which occlusion was an incidental finding Occlusion may be caused by disease of the veins or may occur secondarily to inflammatory, cirrhotic or neoplastic changes in the liver thrombosis in the neighboring vena cava polycythemia vera or debilitating disease which slow the circulation In the 20 cases occlusion was due to thrombosis The condition leads to congestion and atrophy of the liver Usually the region of congestion is not large enough to produce recognizable symptoms If symptoms do arise they are usually masked by the more profound changes of the primary disease Rarely, portal hypertension or even hepatic failure occurs The syndrome may develop

(2) Arch Int M d. 75 175 183 M h 194

slowly or rapidly Outstanding clinical features are pain in the upper part of the abdomen and back enlarged tender liver with latent or mild jaundice enlarged spleen well developed collateral circulation and ascites Disturbance of hepatic function is marked Thrombosis of hepatic veins may be followed by thrombosis of portal and mesenteric veins and infarction of the bowel



FIG 105 (l ft) —At ophy f l ft l l er d hyp t phy f dat l be f
FIG 106 (ght) —S ct on of f r sh w ost uma of hep t e a clud d by rg zed th mb

Hepatic coma rupture of esophageal varices carcinoma or intercurrent infection is the immediate cause of death Diagnosis is usually made at autopsy

Jaundice is rare and if present is mild In the authors four cases there was no visible jaundice slight elevation of serum bilirubin values was found in only two Ascites is common and was present in all four cases paracentesis was necessary in three Edema of the legs occurred in one case it may occur late in the disease as a result of hepatic failure Cyanosis was present during acute episodes in two cases and is probably part of the picture of shock. The four cases were interesting because of the tendency of the disease to progress irregularly Progress was punctuated with sudden devel

opment of a new or exaggeration of an already existent symptom presumably due to extension of the thrombosis Acute episodes are characterized by sharp exacerbation of pre existing pain in the upper part of the abdomen, nausea vomiting cyanosis shock with delirium and finally coma and death In cases of more acute occlusion of the hepatic veins as well as in the acute terminal episodes of the chronic form the rapidity of increase in size of the liver and evidence of profound disturbances of hepatic function and of portal obstruction that could be caused only by some rapidly developing process such as thrombosis, may suggest the correct diagnosis Acute occlusion has been mistaken for acute pancreatitis, but elevation of serum amylase values, rapid liver enlargement and rapid development of portal obstruction should aid in diagnosis

Liver Involvement in Malaria Richard A Kern and Robert F Norris[3] observed liver enlargement in 60 per cent of 1 153 cases of malaria, size of the liver varying from just palpable to easily felt" Enlargement fluctuated with the activity of the disease increasing during an active febrile attack and decreasing after successful antimalarial therapy Jaundice was not usually present When it was present there was muddiness of the scleras only and the van den Bergh test was needed for confirmation The highest reading was 3 5 mg bilirubin per 100 cc Anorexia seemed commonest in patients with enlarged livers and in some appeared associated with nausea and vomiting In a few men anorexia plus malaise and a 'livery appearance suggested mild cachexia There was no generalized itching Subjective pain over the liver was rare although there was tenderness in 8 of 59 men who had a palpable liver The two tests used were the van den Bergh and the bromsulfalein elimination test Usually both gave abnormal findings in the presence of an enlarged liver, the bromsulfalein test appearing to be the more delicate

(3) U S N v M Bull 43 847 858 Nov mbe 1944

In two fatal cases of malaria the liver was examined at autopsy In the first case it was moderately enlarged The parenchyma was swollen and bile stained Lobules were distinct but the centers were pale No areas of necrosis were found microscopically but the parenchymal cells in the centers of the lobules were shrunken and contained excessive amounts of granular yellow pigment Kupffer cells were more numerous than normal and distended with brown and black pigment Anatomic diagnosis was central and midzonal atrophy of the liver In the second case the liver was enlarged and greenish black The parenchyma bulged from the cut section surface and the lobules were indistinct Microscopically parenchymal cells around the central veins had disappeared from nearly all lobules In midzonal and periportal areas they were swollen with indistinct cell walls not only the sinusoids but also the periportal spaces were compressed Kupffer cells containing brown pigment almost filled the lumens of the sinusoids Anatomic diagnosis was acute hepatitis and central and midzonal necrosis of liver lobules The central lobular necrosis of the liver lobules in this case may have been partly caused by the atabrine given parenterally

Presence of liver involvement is not evidence of chronicity it was found as often in the first attack of malaria as in later attacks For evaluation of antimalarial treatment presence of liver enlargement changes in hepatic size and results of function tests may be valuable A high carbohydrate high protein low fat diet seems indicated in malaria to save the liver from further damage

Factors Influencing Ascites in Patients with Cirrhosis of the Liver Elaine P Ralli James S Robson Delphine Clarke and Charles L Hoagland[4] (New York Univ) point out that level of serum albumin has been considered the controlling factor in the accumulation of ascitic fluid in cirrhosis To test this the authors at regular intervals determined plasma levels of albumin and globulin in

(4) J Cl I st g (4 316 3 5 May 1945

patients with cirrhosis who had accumulated ascitic fluid in such quantities that repeated paracenteses were required The patients received an adequate diet and aqueous extract of liver diluted with saline was given intravenously As a result reaccumulation of ascitic fluid was arrested after varying periods in the different patients and further paracenteses were unnecessary The authors could therefore compare plasma levels of albumin and globulin during and after the period of fluid retention Determinations of plasma proteins were also made in patients with severe cirrhosis without ascites

The results indicated that the level of albumin in the plasma is not the determining factor in fluid retention since no significant change in albumin level was notable as long as six months after absence of ascites It seemed possible that the low urine volume in patients with cirrhosis might be the cause rather than the result of water retention Presence of an antidiuretic factor in the urine of patients with nephrosis and premenstrual edema had been reported On the premise that a similar substance might be present in urine of patients with cirrhosis and ascites the antidiuretic effect of aliquots of dialyzed urine from these patients was studied It was found that urine of patients with ascites when injected into hydrated rats delayed excretion of urine Urine from patients without ascites possessed an antidiuretic effect similar to that obtained with the urine from normal subjects Urine of patients in whom ascites had been controlled before assay had an antidiuretic effect greater than the urine of normal subjects but less than that of patients with ascites The nature of the antidiuretic substance obtained from the urine was not ascertained it may have its origin in the posterior pituitary

Disorders of Liver and Extrahepatic Biliary Ducts Associated with Cutaneous Xanthomas and Hyperlipemia George B Eusterman and Hamilton Montgomery[5] (Mayo Clinic) report a case of hepatic cirrhosis

(5) Gastroenterology 3 275 286 October 1944

OTHER TYPES OF LIPIDOSIS ASSOCIATED WITH HEPATIC DISEASE

CLINICAL TYPE	USUAL AGE INCIDENCE	LIPID ABNORMALITY	CUTANEOUS XANTHOMA	LIVER	SPLEEN	RESPONSE TO TREATMENT
Chronic pancreatitis	Adults	Neutral fats + Cholesterol +	Xanthoma tuberosum	Enlarged	Normal	Fair
Arsenical hepatitis	Adults	Cholesterol + Phosphatids + Total lipids +	Xanthoma tuberosum	Enlarged	Moderately enlarged	Poor
Xanthoma diabeticorum	All ages	Hyperlipemia Cholesterol ++	Xanthoma tuberosum	Enlarged and fatty	Enlarged at autopsy	Good
Hepatosplenomegaly lipidosis (Burger and Grutz)	Any age	Cholesterol ++ Phosphatids ++	Xanthoma tuberosum of skin and mucous membrane	Great enlargement	Great enlargement	Fair to poor
Lipoid proteinosis (Urbach)	Infants or children adults occasionally	Lecithin increased +	Xanthoma of mucous membranes lichenified infiltration of skin	Rarely involved	Normal	None

multiple xanthoma tuberosum of the skin and severe hyperlipemia

Woman 48 complained of severe refractory, generalized intense pruritus continuous aching pain and hyperesthesia especially in both extremities cutaneous yellow nodules, gastro intestinal dis turbances loss of weight and strength yellowing discoloration of the skin and severe physical and nervous exhaustion of over two years duration Enlargement of the liver and jaundice had been found previously There was a history of alcoholic abuse for the previous 10 years

Examination showed icterus anemia and cachexia of moderate degree and generalized xanthochromia especially of forehead face neck and thorax Yellow nodules infiltrations and plaques were present all over the body The liver was enlarged firm insensitive and not particularly *nodular* *Biliuria* grade 1, was present There was marked superficial tenderness to pressure on the forearms hands and feet Value for serum bilirubin was 5 mg per 100 cc and the van den Bergh reaction was direct The bromsulfalein test dis closed grade 4 (most severe) retention of dye The albumin globu lin ratio was lowered and severe hyperlipemia was present Roent gen examination showed bronchiectasis of the lower lobes of the lung Tentative diagnosis of xanthomatous biliary cirrhosis was made with unfavorable prognosis Despite treatment there was slow progressive decline with death

Autopsy showed multiple erosions of cardiac and esophageal varices with massive hemorrhage into the gastro intestinal tract reticulum cell hyperplasia of the spleen broncho stenosis of the main bronchus of the lower lobe of the left lung with marked bronchiectasis complicating purulent bronchitis and diffuse pneu monia at bases of both left lobes xanthoma tuberosum and gen eralized atheroma of the larger arteries The liver was enlarged and micro copically the cirrhosis was more of the biliary than of the atrophic type Bile ducts appeared small and squeezed out rather than dilated There was periductal rather than periportal distribution of inflammation and fibrosis

The long standing jaundice hypercholesteremia ab sence of ascites atrophy and nodularity and gross and microscopic appearance favor biliary rather than atrophic cirrhosis despite a history of chronic alcohol ism The exact cause of cutaneous or systemic xantho matosis is still undetermined Other lipoidoses associated with hepatic disorders important in differential diag noses are listed in the table

Hemochromatosis Joseph T Beardwood Jr and George P Rouse, Jr[6] (Philadelphia) report that in over 5 000 cases of diabetes mellitus they found only 2 cases of hemochromatosis proved by biopsy and 1 case in which the condition was strongly suspected These three cases are reported in detail The first case presented a fairly typical clinical picture while the second case was unusual in that the patient was a woman occurrence in females being exceedingly rare and the additional com plications of thyroid dysfunction and hypertension were present In the third case the patient clinically had hemochromatosis but skin biopsy showed an unusual type of iron metabolism in all nuclei a type not usually characteristic of this condition

In Cases 1 and 2 the method described by Fishback for clinical demonstration of iron in the skin was used

TECHNIC —Equal parts of sterile solutions of 0 5 per cent potas sium ferrocyanide and N/100 h drochlor c acid are combined and injected int ad rmallv so as to form a wheal A positive reaction is present f a slight blue color appears almost immediately and darkens to a deep blue w thin an hour A narrow red zone appears at th periphery of the wheal and persists throughout the slow con struction of the blue te t spots until t has completely faded in about two weeks A negative eaction evidenced by a white wheal with the peripheral red zone the latter fades in about two weeks the front spiece to this YEAR BOOK shows both positive and control reactions The test appears to be harmless and specific for this dis ease It is s mpl and econom al and takes little time

Treatment consists only of control of the diabetes which is sometimes difficult The authors have found no cases in which the skin discoloration cleared with con trol of the diabetes

Clinical Significance of Palpable Spleen is discussed by William F Lipp Ellen H Eckstein and A H Aaron[7] (Univ of Buffalo) Of 2 274 consecutive pa tients most of them with chronic rather than acute dis ease who were repeatedly examined 128 had a palpable spleen Sex was about equally divided and ages were

(6) Cl n 3 51 60 A gu t 1944
(7) G t t l gy 3 28 91 O t ber 1944

between 20 and 60 years Italian patients had the high est incidence of palpable spleens The 128 patients were divided into two groups group 1, 34 patients with dis eases in which enlargement of the spleen generally oc curs group 2 94 patients in whom there was some ques tion as to etiology of the palpable spleen In group 1, 4 patients had diseases of the reticulo-endothelial sys tem 4 *infections* 15 *hepatic diseases* 5 *metastatic* car cinoma involving the liver and 6 congestive heart fail ure In group 2 there were 13 with cholelithiasis 15 with visceroptosis 13 with suggestive evidence in their histories and 53 with no evidence to explain the splenic enlargement despite careful laboratory and history stud ies Possibly the enlargement in the last group repre sents a residuum of certain infections during childhood such as scarlet fever a viral disease or unremembered catarrhal jaundice

The finding of a palpable spleen may influence future diagnostic studies in a given patient and should be re corded This finding is of special interest in that mem bers of the armed services are returning from war zones where tropical diseases are endemic

Courvoisier's Law in Regard to Gallbladder Robert Elman[8] discusses the monograph on pathology and surgery of the biliary tract published by Courvoisier in 1890 in which the condition of the gallbladder is described in 187 cases of obstruction of the common duct with jaundice In 87 cases obstruction was due to stones and in 70 of these there was a contracted gallbladder The gallbladder was dilated in 92 per cent of the re maining *100 cases in which obstruction was not caused* by stones Courvoisier s explanation was that infection of the gallbladder nearly always present with stones produced so much fibrosis that distention was impossible With the other types of obstruction due largely to car cinoma infection was not present and the thin walled gallbladder dilated After 1900 Cabot reported an even

(8) G stroe t ology 3 416-417 N ember 1944

closer correlation between size of the gallbladder and type of obstruction Among 57 cases in which obstruction was due to a stone in the common duct there were *only 2 in which the gallbladder was enlarged* whereas among 29 cases with obstruction due to cancer of the head of the pancreas there were only 2 in which the gallbladder was not distended Thus only 4 of 86 cases violated the rule now known as Courvoisier s law

This law is of considerable aid in differential diagnosis in a case of jaundice Such diagnosis may be difficult at the bedside as well as at laparotomy While the *law is valuable at the bedside whenever examination* shows an enlarged gallbladder such a finding is made with certainty only when the abdomen is opened Thus Courvoisier s law is useful largely at the operating table Its exceptions are probably due largely to stones being associated with carcinoma Another exception is presented by a carcinoma of the common duct above the entrance of the cystic duct which is always associated *with a collapsed gallbladder* even though there are not stones

Analysis of Reaction of Human Gallbladder and Sphincter of Oddi to Magnesium Sulfate Edward A Boyden George S Bergh and John A Layne[9] (Univ of Minnesota) examined 18 volunteers by routine oral cholecystography and found gallbladder shadows strong enough to be traced in 14 who underwent further study *Films were made after passage of a Rehfuss tube* and 30 cc saturated solution of magnesium sulfate was then injected (into the duodenum in 10 and into the stomach in 4) Roentgenograms were made 2 4 8 12 16 20 25 30 35 40 and 45 minutes after injection The gallbladder shadows were traced changing volumes computed and individual curves of evacuation plotted Percentage loss in volume and mean values were established and compared with *mean curves obtained in earlier studies of* reaction of the gallbladder to egg yolk

(9) S g ry 13 3 733 M y 1943

Results showed that while magnesium sulfate is effective in evacuating the human biliary tract, it is inferior to egg yolk Average decrease of 42 per cent in gall bladder volume and lowering of sphincter resistance by 3 cm water were obtained with magnesium sulfate whereas egg yolk lowered gallbladder volume 71 per cent and sphincter resistance 7 cm Thus magnesium sulfate acts as does egg yolk, differing only in degree which difference is probably due to slower absorption rate or less effective chemical action Thus both magnesium sulfate and egg yolk are to be considered hormone producing substances which act independently through the blood stream on both gallbladder and sphincter of Oddi

However the two organs react differently to a given stimulus Initially a dose of either egg yolk or magnesium sulfate usually causes the sphincter to contract This in turn may interrupt the contraction of the gallbladder which is just beginning thereby producing the so called two minute pause After 4 or 5 minutes however the sphincter enters a period of progressive relaxation which lasts for an average of 17 minutes Meanwhile the gallbladder begins its main phase of contraction which lasts for an average of 30 minutes Animal experimentation suggests that the hormone acts on the sphincter for a shorter time than on the gallbladder because during fasting sphincter tone is maintained by a local nerve net which has a higher threshold than that of the gallbladder

Analysis of Duodenal Drainage in Steatorrheas Herbert F Philipsborn Jr Grace Lawrence Stanley Gibson and Harry Greengard[1] (Northwestern Univ) studied groups of normal children children presenting feeding problems children with fibrocystic disease and children with celiac disease to set up criteria for diagnosis of fibrocystic disease of the pancreas and celiac disease two conditions which resemble each other closely

(1) J Ped t 6 107 119 February 1945

but differ in their management and their prognosis

Stools and vitamin A curves in celiac disease may closely resemble those in fibrocystic disease Quantitative analysis of duodenal drainage for enzymatic activity coupled with notation of the pancreatic response to secretin or intraduodenal hydrochloric acid is the most reliable laboratory aid in differential diagnosis Feeding problems may be on the basis of a temporary pancreatic insufficiency Permanent pancreatic insufficiency with infantilism must be differentiated from celiac disease fibrocystic disease and certain types of feeding problems The value for tryptic activity is the most reliable index of pancreatic function Values of less than 4 Gm liberated nitrogen per 100 cc duodenal fluid are abnormal for children Less than 0 5 Gm liberated dextrose per 100 cc duodenal drainage during the first 12 months of life is abnormal less than 2 Gm after 1 year of age is abnormal When less than 60 cc N/20 sodium hydroxide is required to neutralize free fatty acids produced by the lipolytic activity of 100 cc duodenal fluid pancreatic lipase is considered diminished Enzymatic activity in the duodenal drainage is markedly diminished in fibrocystic disease it remains essentially normal in celiac disease Response to intravenous secretin or intraduodenal N/10 hydrochloric acid is reduced in fibrocystic disease but may remain normal in celiac disease and transient and permanent hypochylia pancreatica

Steatorrhea Due to Lymphatic Obstruction R S Bruce Pearson[2] enumerates conditions in which fat is found in excess in the stools sprue nontropical sprue idiopathic steatorrhea adult celiac disease celiac disease steatorrhea due to lymphadenopathy intestinal lipodystrophy steatorrhea with chyladenectasis pancreatogenous steatorrhea and gastrocolic fistula with steatorrhea He reports three cases to emphasize the similarity between idiopathic steatorrhea and steatorrhea due to lacteal obstruction

(2) Pro R y S Med 38 85 387 M y 1945

Case 1 presented features in common with idiopathic steatorrhea—high fecal fat, sore tongue and macrocytic anemia Tetany was never demonstrated Diagnosis depended on appearance of glands above the clavicle, irregular pyrexia x ray appearance of the chest and positive Mantoux reaction all of which pointed to tuberculous lymphadenopathy In Case 2 high fecal fat, low serum calcium and protein and terminal hemorrhagic condition, probably due to failure to absorb vitamin K were present Blood sugar curve was normal however anemia was slight and pyrexia intermittent Dilated lymphatics indicated obstruction of lymphatic flow, although its exact site was not demonstrated The condition was clearly inflammatory in origin and the presumption was that a chronic abdominal abscess was responsible for maintaining a low grade inflammatory process with consequent lymphatic obstruction Case 3 which closely simulated idiopathic steatorrhea presented steatorrhea macrocytic anemia low serum calcium with tetany low serum protein flat sugar curve sore tongue and terminal hemorrhagic tendency Autopsy diagnosis was reticulosarcoma Thus all three cases showed some clinical features usually associated with idiopathic steatorrhea The flat sugar curve in one case and low serum protein in two indicate that although the primary lesion may be in the lymphatic system the absorption of food substances other than fat is indirectly affected

Ascariasis of Bile Ducts Rudolf Guhl[3] (Univ of Zurich) points out the tremendous increase in incidence of human ascariasis in Europe caused mainly by war conditions such as increased consumption of vegetables salads and fruits *increase in gardening with fertilization* by human excreta and lack of cleanliness due to lack of soap Two cases are reported with autopsy observations in the first severe ascariasis was found in the bile ducts and liver The second case occurred in a woman, 71 who

(3) Schweiz med Wchnschr 74 600 605 June 3 1944

had abdominal pains chills icterus and hepatic pains There was no history of ascariasis but stool and bile contained ascaris eggs (Fig 107) Peritonitis and cholangitis developed Autopsy revealed ascariasis of the bile ducts multiple liver abscesses a subphrenic abscess and peritonitis (Fig 108)

The manner in which ascarides penetrate the bile ducts and the effect of cholelithiasis in predisposition of the

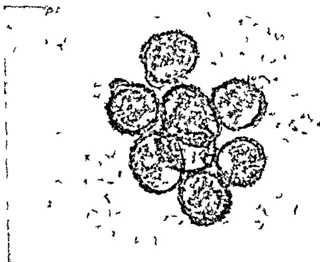


Fig 107 —A eggs in bil from g llbladd

bile ducts to ascarides are not clear Ascarides are found more often in European women than in men but more frequently in Japanese men than in women Their main site in the bile ducts is the ductus choledochus and less frequently the hepatic ducts and intrahepatic branches Mechanical sequelae include dilatation and subcapsular lesions of the bile ducts and cholangitis Severe colics are caused by the reflex mechanisms Ascaris intoxication and probably al o biliary cirrhosis are due to the toxins

stone formation may occur Symptomatology is similar to that of cholelithiasis and cholangitis and diagnosis is difficult Treatment consists of surgical removal of the ascarides and drainage of the ductus choledochus and



FIG 108 —Sto and a c de n duct s holedochu one ascaris also in Vater s pap ll

hepaticus with complete deworming of the intestines

Serum Amylase Findings in Chronic Alcoholic Patients with Acute Severe Abdominal Symptoms Sylvester J Carter[4] (Harlem Hosp) reports 11 cases with histories of chronic alcoholism and abdominal symptoms including vomiting severe epigastric pain and marked rigidity of abdominal muscles especially in the upper half of the abdomen with or without epigastric tender

(4) Ann Su g 12 117 1 1 July 1945

ness on physical examination This type of case has been called acute alcoholic gastritis by the hospital staff Not infrequently an unnecessary exploratory celiotomy has

SERUM AMYLASE FINDINGS IN 11 PATIENTS WITH ALCOHOLISM AND ACUTE ABDOMINAL SYMPTOMS

CAS	OPERATION	SERUM AMYLASE	URINE AMYLASE	PERITONEAL FLUID AMYLASE
1	Findings thin sanguneous fluid in abdominal cavity edema about pancreas			
1 (readmiss on)	None	340		
	None	607		
(readmiss on)	Find ngs thin sanguineous fluid in abdominal cavity edema about pancreas	844		415
3	Findings thin sanguineous fluid in abdominal cavity eden a about pancreas	350	35	990
4	Find ngs thin sanguineous flu d in abdominal cavity edera about pancreas	68		
	None	488		
5 (readmiss on)	None	48		
6	None	94	700	
	None	385	1024	
8	None	455		
9	None	3		
10	None	80		
11	None	3 0		

Som gy u t

been done for a possible surgical lesion

Clinically the lesion seemed to be in the stomach in some cases while in others the pancreas appeared involved The last alcoholic debauch evidently precipitated changes in a digestive system impaired by prolonged use of alcohol Sometimes symptoms were much more severe than could be explained by simple acute gastritis superimposed on chronic gastric pathology

stone formation may occur Symptomatology is similar to that of cholelithiasis and cholangitis and diagnosis is difficult Treatment consists of surgical removal of the ascarides and drainage of the ductus choledochus and



FIG 108 —Stone a d d d ct s choledo h s o s a ls
\ t s p p ll

hepaticus with complete deworming of the intestines

Serum Amylase Findings in Chronic Alcoholic Patients with Acute Severe Abdominal Symptoms Sylvester J Carter[4] (Harlem Hosp) reports 11 cases with histories of chronic alcoholism and abdominal symptoms including vomiting severe epigastric pain and marked rigidity of abdominal muscles especially in the upper half of the abdomen with or without epigastric tender

(4) A n Su g 1 2 117 1 1 July 1945

Biliary tract disease was present in eight cases There was acute noncalculous cholecystitis in two cases acute calculous cholecystitis in one stones in the gallbladder in one and stone in the common duct with previous common duct stricture and cholecystoduodenal fistula in one Two of the three patients not treated surgically gave a

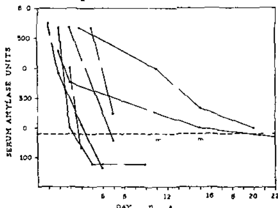


FIG 109—C rves sh w lev ted m myl during cute ttack, with f ll att k ub des

definite history of biliary tract disease and in one stones were found at autopsy (Fig 110)

The hemorrhagic type of acute pancreatitis was present in six cases in three of these associated conditions were acute pancreatic abscess a large pancreatic cyst and early hemorrhagic cyst formation respectively This is in contrast to reports in the literature which state that the edematous form is more common This suggests that milder cases may have been missed Serum amylase tests should be made in all cases of obscure acute upper abdominal pain as a means of establishing the correct diagnosis

Leukocytosis was present at admission in eight cases In four white cell count and serum amylase values were correspondingly elevated In two cases white cell counts were normal despite elevated serum amylase values In

Four operations were performed and in each instance edema around the pancreas and peritoneal fluid of thin sanguineous character were found (see Table) In the other cases the high amylase values were the chief factor in deciding against intervention These seven patients were discharged well Elevated serum amylase is considered due to rapid destruction of the acinar membranes of the pancreas with sudden overflow of the enzyme into the immediate surrounding pancreatic tissue which cannot hold or confine it and thus escape of the enzyme into the blood stream Its presence in urine and peritoneal fluid can be similarly explained Carter recommends therefore that serum amylase determinations be made on all patients with chronic alcoholism if surgery is contemplated because of severe acute abdominal symptoms

[This is a timely article considering the heavy increase in consumption of alcohol in this country In 1938 Weiner and Tennant called attention to the relationship of alcohol to acute hemorrhagic pancreatitis and chronic pancreatitis as well on the basis of post mortem findings The use of alcohol intravenously as an anesthetic agent has also brought this relation hip into sharp focus recently —Ed]

Conservative Management of Acute Pancreatitis Thomas A Shallow Sherman A Eger and Frederick B Wagner Jr[5] (*Jefferson Med College Hosp*) report 12 cases illustrating the value of this type of therapy

Serum amylase findings confirmed the value of the test for diagnosis (Fig 109) In all cases in which the *determination was made at the height of the attack or* within 48 hours of acute onset, the level was definitely elevated In two cases normal values were obtained but in these determinations were made on the fourth and the *fourteenth* day confirming the fact that the value may fall to normal within 12–24 hours and thus fail to prove the true nature of the disease In six cases in which serial determinations were made the values fell as the attacks subsided In two cases, the pancreas felt essentially normal at operation but in both operation had been delayed for 22 and 15 days after onset

(5) Pennsylvania M J 47 1193 1 09 September 1944

pancreas head with resultant compression of the common duct in its transit through the gland In some cases a stone in the common duct or associated hepatitis may play a role In five of the seven cases in which prothrombin determinations were made the value was 60 per cent or less In several cases the bromsulfalein excretion test showed mild degrees of dye retention These findings indicate the frequency of associated liver damage probably toxic in origin Low serum protein values were found in four of the seven cases in which this determination was made

There have been no deaths in this series in two years In three cases correct preoperative diagnosis was made but operation was delayed while toxemia hypoproteinemia and associated liver damage were treated In two other cases the condition improved under conservative therapy so that operation was unnecessary In five further cases in which the lesion was unexpectedly encountered at laparotomy the most conservative procedure aimed at correction of any obviously contributing defect was done In one case with correct preoperative diagnosis operation might have been avoided if the serum amylase value had been elevated at the late date at which it was taken (two weeks after acute onset) although during this time symptoms persisted One other case was of the fulminating type but operation could not be done *because of the patient's poor condition*

If the clinical picture of acute pancreatitis is substantiated by elevated serum amylase value operation should be delayed and sometimes not done Conservative and preoperative management include use of oxygen in severe cases Wangensteen suction saline and glucose intravenously blood plasma and amino acids to correct hypoproteinemia and vitamin K In the necrotizing type sulfonamides may be indicated but the additional toxic effect must be remembered If systemic symptoms do not respond to the usual administrations use of sulfonamides is indicated

two others white cell counts were elevated with normal amylase values These results suggest that the serum amylase value may be elevated during the early stages before the leukocytic response occurs whereas the leuko-

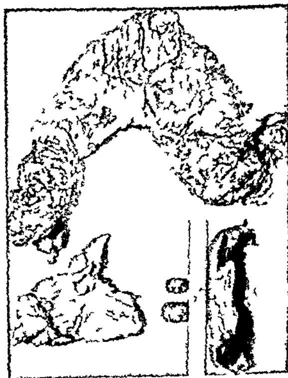


FIG 110 — Po tm rt m I h w ng f t ecr f m r m a d per a dium ta t h m lag a d two large g llst e

cytosis may persist for several days after serum amylase values have returned to normal Slight to marked albuminuria was present in all but two cases This albuminuria is probably caused by an irritant effect of the circulating toxic products on the renal glomerular membrane or the tubular epithelium Increase in serum bilirubin was found in seven cases it ranged from latent to manifest jaundice and is probably due to edema in the

Dietary Factors in Treatment of Cirrhosis without Jaundice A B Rimmerman Steven O Schwartz Hans Popper and Frederick Steigmann[7] (Cook County Hosp) point out that cirrhosis appears to be a deficiency disease rather than an intoxication They therefore analyzed the effect on cirrhosis of a diet rich in protein and carbohydrates and low in fat supplemented by choline and vitamin B complex The effect was judged by liver function tests (Table 1) blood examinations and in some cases marrow examination Ten patients were given the diet shown in Table 2 All tests were done before the diet was started and were repeated after one week If results were almost identical the patients were placed on the diet All tests were repeated at weekly intervals The patients were kept hospitalized as long as possible or until improvement appeared after dismissal they returned for monthly examinations

Little change was noted for four weeks after beginning treatment In 6–16 weeks definite improvement subjective and objective was noted In two patients ascites and edema remained unchanged after 4 and 5 weeks in four ascites and edema were decreased after 6–16 weeks in the remaining four ascites and edema had disappeared after 6–16 weeks Total protein increased in six cases and albumin fraction in five In two cases there wa decrease in albumin and in four decrease in globulin Percentage of cholesterol esters increased in six cases hippuric acid excretion increased in only four Reactions to the Takata Ara and cephalin cholesterol flocculation tests remained unchanged in patients who otherwise showed improvement The hematologic picture showed improvement in only three cases but subjectively four patients improved remarkably and five somewhat and only one remained unchanged

Of four similar patients used as controls on the routine diet three showed no change and one showed increase in ascites and edema Total protein decreased in

(7) Am J D gest D 11 401 404 D mbe 1944

Acute Pancreatitis John Morton[6] (Univ of Rochester) reports 18 cases and summarizes the salient factors of the disease The five principal contributing causes are (1) trauma accidental or surgical, (2) infections with extension to pancreas or biliary tract, (3) toxic agents such as alcohol drugs (arsphenamine) and anesthetics (4) *biliary obstructions such as stone, spasm* infection tumor and duodenal diverticulum, and (5) circulatory factors such as stasis hypertensive apoplexy thrombosis and embolism The serum amylase test is of great aid in deciding whether the pancreas is involved

Clinically there are two distinct pathologic types of acute pancreatitis The commoner type acute edematous pancreatitis (interstitial pancreatitis) is manifested by a boggy swollen pancreas with fluid under tension and may be accompanied by fat necrosis It usually subsides spontaneously in most cases if let alone The other type, hemorrhagic necrosis is a serious disease with death of a large part of the organ Acute edematous pancreatitis can be diagnosed by the serum amylase test and by rapid improvement under conservative treatment Pancreatic necrosis must be suspected if the patient fails to improve in a few days Operation is deferred in acute edematous pancreatitis until the reaction has subsided whereas conservative treatment of pancreatic necrosis or pancreatic abscess which follows pancreatic necrosis is disastrous When presence of the latter is suspected operation is indicated as soon as possible

Biliary disease should be treated after an attack of acute pancreatitis if it has played a part in the onset Any surgical manipulation about the lower end of the common duct or head of the pancreas is likely to be followed by acute pancreatic edema There is considerable danger of this condition in resection of posterior duodenal ulcer which has perforated into the pancreas It carries a mortality which should be taken into consideration in any series of duodenal ulcer resections

(6) S gery 17 475-491 April 1945

TABLE 2.—SOLID (MEAT FREE) DIET*

	AMOUNT GM	PROTEINS	F TS	CAR O HYD TES
Breakfast				
9% fruit	00		–	18
Cooked c real	200	4	2	16
Sugar	10	–	–	10
Toast	40	4	–	21
Butter	10	–	9	—
Egg	1	6	6	—
Coffee				
Sugar	10	–	–	10
Milk	00	6	8	10
9 00 a m				
Milk	100	3	4	5
Brewers yeast	25	1	–	10
Dinn r				
Egg	1	6	6	—
vegetable	100	2	–	3
6% vegetable	100	2	–	6
18 vegetable	100	3	–	18
Bread	0	3	–	16
Butter	6		5	—
1 % fru t	150		–	18
Sugar	20			0
Milk	00	6	8	10
Jello	100	3	–	–
00 p m				
Brewers yeast	25	12	–	10
Milk	100	3	4	5
00 p m				
D etene	50	16	–	28
Milk	1 0	5	6	8
Crackers	2	1	1	5
Lec thin	15	–	–	—
Supper				
vegetable	100	2	–	
6% vegetable	100	2	–	6
18% ve etable	100	3	–	18
3% fruit	00	2	–	18
Sugar	20	–	–	20
Bre d	0	3	–	16
Butter	6	–	5	—
Milk	200	6	8	10
8 00 p m				
D etene	50	16	–	20
Milk	150	5	6	8
Crackers	2	1	1	5
Le ithin	15			

Th tot l m t f prot w 141 f t 79 bohyd t 401 d al es 2 879 100 Gm m f b hydrates i g a 10 p ce t (h gh) dext l t n i t ly

TABLE 1.—Findings in Patients with Cirrhosis without Jaundice 10 on Special Diet with High Vitamin Supplements and 4 Controls*

Weeks under Observation	No. of Exam	Ascites Edema	Total Protein		Albumin		Globulin		Cholesterol Esters		Hippuric Acid Excretion		Hematologic Picture	Improvement	
			Before	After	Before	After	Before	After	Before	After	Before	After		Subjective	Objective
4	1	Unchanged	7 0	7 3	4 0	2 6	2 0	4 7	69	51	0 9	1 0	Unchanged	Unchanged	Unchanged
8	3	Decreased	6 9	7 8	2 6	2 7	4 3	4 9	28	8	1 3	1	Unchanged	Moderate	[illegible]
6	2	Disappeared	4 0	7 0	2 6	1 4	3	3 6	39	73	1 2	1 4	Unchanged	Marked	Moderate
4	2	Disappeared	7 0	7 0	3 5	4 0	3 5	3 0	53	84	3 5	3 5	Improved	Marked	Moderate
16	4	Decreased	5	5 5	3 0	4 0	2 7	1 5	81	0	2 5	2 6	—	Moderate	Moderate
8	3	Decreased	4 4	5 4	2 9	9	1 5	2 5	31	63	1 4	4	—	Marked	Marked
16	4	Disappeared	5 0	8	6	5 5	2 4	3 2	41	93	1 7	3 7	Unchanged	Marked	Marked
3	2	Disappeared	6	9 0	2 3	4	5 3	4 3	32	60	3 1	3 8	Improved	Marked	Marked
4	1	Unchanged	8 0	7 0	3 1	3 3	4 9	3	45	33	2 0	2 1	Unchanged	Slight Improvement	Slight Improvement
6	2	Decreased	7 3	8 6	3 8	4 2	3 6	4 3	53	56	2 6	3 6	Improved	Moderate	Moderate
Controls															
0	2	Unchanged	7 2	6 8	4 3	3 8	2 9	2 0	51	50	—	2 1	—	Unchanged	Unchanged
4	2	Unchanged	6 4	7 6	3 2	4 7	3 2	2 9	71	3	2 4	2 8	Decreased	Unchanged	Unchanged
4	2	Unchanged	5 8	7 6	2 6	3 8	3 2	4 0	59	—	2 3	2 0	Decreased	Worse	Dead
4		Increased	6 6	4 7	3 2	3 5	3 4	1 2	42	47	4	2 5	—	Unchanged	Unchanged

* T kata-Ara eact n ma d h r g d ceph l n-cholesterol floccul t eact n m ined unch nged the ne case wh h th test was o d ur nary ur bil og n h ed o g h t ha ge.

choline was thus given after meals However when three patients after an overnight fast were given 0 5 Gm choline chloride without food one patient had nausea and a slight drop in blood pressure with slight slowing of the heart rate

[The efficacy of th s preparation has been challenged in some quarters Choline is al o a constituent of brewers yeast Peppermint water as a veh cle sweetened with saccharin s one to which few patients object Choline can also be administered in capsules —Ed.]

Use of Theophylline Ethylenediamine (Aminophylline) for Relief of Biliary Colic Arthur Gladstone and Louis Goodman[9] (Univ of Vermont) observed effects of aminophylline injected intravenously in eight cases of acute biliary colic Dose was 0 25–0 5 Gm and pain was relieved within 2–20 minutes There were no after effects In one case aminophylline was used to obtain specimens of gallbladder bile during duodenal intubation when the usual methods of instillation of magnesium sulfate solution olive oil and peptone failed The dose in this case was 0 5 Gm injected intravenously at a slow rate Immediately after completion of injection an active flow of dark concentrated bile was obtained there were no ill effects

Protective Liver Therapy with Water Soluble Percorten administered intravenously is discussed by A Kappert[1] The cortical hormone acts on the carbohydrate metabolism and the mineral and hydrogen metabolism of the liver To avoid harmful side effects with the necessarily large doses of percorten sodium chloride ingestion should be limited to 4 or 5 Gm daily

Severe cases of epidemic hepatitis have been treated by this method In such cases a closure type of jaundice occurs caused by intrahepatic edema and in some cases by an additional spastic process of the gallbladder system These factors explain the success with percorten therapy and epidural anesthesia The percorten injections fail in about 20 per cent of cases of severe hepatitis probably due to swelling of the portal lymph nodes and

(9) J A M A 1 6 1084 1085 D 23 1944
(1) S hwei m d W hn h 74 569 573 M y 7 1944

two and slightly increased in the other two Cephalin flocculation decreased in two increased in one and remained unchanged in one The globulin fraction decreased in all four cases and the cholesterol ester ratio in one case Hippuric acid excretion decreased in one, increased in one and remained stationary in two Clinically three patients showed no change and one died

The authors conclude that the diet produced definite improvement as measured by the liver function tests in some of their patients

Choline As Adjuvant to Dietary Therapy of Cirrhosis of Liver A H Russakoff and Harold Blumberg[8] (Baltimore) report on 10 patients studied in two years All had decompensated portal cirrhosis of the liver and were treated with a high caloric, high protein high carbohydrate low fat diet the usual vitamins and, in addition choline

Four of the patients are dead Of the six living, three are free from ascites The other three still have ascites but have improved somewhat One patient with a small shrunken liver and ascites of at least two years duration was hypoproteinemic and required abdominal paracentteses every four weeks prior to admission On the prescribed regimen and with a unilateral saphenoperitoneal anastomosis he goes 16 weeks without abdominal tapping Another patient improved remarkably and has been at vigorous work with only a small amount of ascites The third patient was able to return to work In six cases diet alone was tried for several weeks without benefit In three of these obvious responses were noted within a week after addition of choline, and probable responses were subsequently noted in two of the other patients Choline was given in small doses at first but later as much as 6 Gm choline chloride was given daily in divided doses Peppermint water was used as solvent for flavoring and to avoid using even the smallest quantity of alcohol No unfavorable reactions were found when

(8) Ann Int Med *1 848 86 N ember 1944

diet and bile salts preferably the oxidized bile salts

Surgery is contraindicated in cases of chronic cholecystitis without typical attacks of biliary colic and with a stoneless gallbladder in 40–50 per cent of cases A conservative therapeutic regimen of a bland diet with uncooked fats in quantities tolerated antispasmodics and bile salts is recommended

Several factors must be considered in treatment of cholecystitis without colic but with calculus Surgical mortality increases with the patient s age Complications such as a fistula between gallbladder and adjacent viscera due to pressure erosion by a large stone develop in a considerable number of patients Carcinoma of the gall bladder probably occurs more frequently in stone bearing gallbladders than in others Conservative management consists of periodic supervision prevention of spasm by antispasmodics regulation of bowel habits through use of a bland diet and careful adjustment of the uncooked fat content of the diet to prevent unnecessary gallbladder stimulation

Patients with gallstones and frequent attacks of colic should be treated surgically by cholecystectomy as the only way of achieving relief

For prevention of spasm atropine or atropine derivatives such as belladonna give best results Cathartics are contraindicated Uncooked fats such as butter eggs *cream or cheese are usually tolerated many of Dolkart s* patients did well on hourly feedings of milk and cream

[By and large the nonsurgical treatment of organic cholecystic disease is circumscribed Even though the disturbances may be infrequent and often of indirect or reflex nature surgical intervention should be seriously considered when demonstrable evidence of this highly prevalent disease exists Too often the conservative internist s recommendation against operative intervention or postponement is not to the patient s ultimate best interests —Ed]

severe histologic changes in the hepatic tissues A combination of percorten with glucose appears most successful An infusion is made of 300–500 cc of a 5 per cent glucose solution with 10–50 mg water soluble percorten, these infusions are repeated as needed at intervals of one to several days Injection by syringe of 10 mg water soluble percorten and 20–50 cc of a 20 per cent glucose solution daily at beginning of treatment seems best Results and effect are quickly noticeable

Intravenous administration of percorten is indicated in every type of parenchymatous liver damage and is useful in treatment of epithelial decompensation in liver cirrhosis It is effective in cases of cholangitis with parenchymatous damage Prophylactically it is useful in cirrhosis if there are bacterial infection of the liver and danger of acute hepatic collapse

[A therapeutic procedure with which we here in America are more or less unfamiliar and which may prove worthy of trial —Ed]

Medical Treatment of Biliary Tract Disease Ralph E Dolkart[2] (Northwestern Univ) recognizes five main varieties of biliary tract disease the so called group of biliary dyskinesias chronic noncalculous cholecystitis, calculous cholecystitis without colic, calculous cholecystitis with colic and acute cholecystitis with empyema The last condition is essentially surgical and it is generally recognized that an acutely inflamed gallbladder should be removed when diagnosed

The somewhat indefinite diagnosis of biliary dyskinesia is based on vague gallbladder symptoms vague bowel symptoms no history of colic and poor filling or poor emptying of the gallbladder on x ray examination Priodax a new gallbladder dye in tablet form gives promise of better results in visualization and less irritation of the gastro intestinal tract Improved aids in diagnosis such as this will result in less frequent diagnosis of biliary dyskinesia possibly the symptoms arise from a disturbed bowel rather than from a disturbed gallbladder Therapy includes antispasmodics a high fat, bland

(2) Illinois M J 87 43 45 January 1945

medium as they gave positive results and since there was marked inhibition of coliform organisms, examination of the cultures was simpler

Trial with pure cultures showed that desoxycholate medium suppressed almost completely most coliform organisms and to a lesser extent the paracolon and atypical coliform organisms it had little action on proteus strains All types of dysentery organisms grew well Growth of Sonne strains was interesting Leifson thought that these organisms were inhibited The Wilson and Blair medium also was superior to the MacConkey medium Therefore there is no justification for continued use of the MacConkey medium in examination of feces for the dysentery organisms The desoxycholate medium must be carefully prepared and controlled for successful results

Control of Bacillary Dysentery is discussed by R W Fairbrother[4] The incidence of bacillary dysentery carriers and intermittent excretion of Bacterium dysenteriae by carriers were readily demonstrated by using the desoxycholate citrate medium with the technic here described

TECHNIC —Samples of feces usually received with n one or two hours of collection were thoroughly suspended by sterile glass rods in small amounts of physiologic saline The thick suspensions were then plated onto desoxycholate citrate plates in case of fluid feces cultures were prepared directly with flakes of mucus After overnight incubation at 37 C suspicious colonies were selected for biochemical and serologic tests all plates were then reincubated for another 24 hours If no suspicious colonies were found a negative result was reported

Italian prisoners of war were used for this study Results indicate that the carrier state in bacillary dysentery is relatively common and persistent in many cases the acute stage of the disease had occurred two or three years previously The carrier state seldom produces symptoms and therefore clinical evidence of its existence is absent Results also suggest that sulfaguanidine is satisfactory for treatment of dysentery carriers, how

(4) B M J 2 489 49 Oct 14 1944

Selective Mediums for Isolation of Bacterium Dysenteriae To test the relative value of mediums for isolation of dysentery bacilli from the feces of carriers R W Fairbrother[3] studied specimens from men who had come from the Middle East and who gave a definite history of bacillary dysentery one to three years previously Samples of feces were emulsified with an approximately equal part of saline and after the heavy particles had settled the following mediums were heavily seeded MacConkey desoxycholate citrate and Wilson and Blair After overnight incubation, suspicious colonies were subcultured and subjected to biochemical and serologic tests The latter were done by slide and by macroscopic agglutination with complete agreement

Six cases of active dysentery were under observation In none were the feces examined until the third or fourth day of illness Bacterium dysenteriae was isolated in four cases three being Flexner strains and one Sonne In each case pure cultures were obtained with the desoxycholate medium while with the MacConkey medium many coliform organisms were also present, Wilson and Blair s medium was not used Feces were collected from 260 patients with recent attacks of dysentery They were examined in two batches The first 154 samples from 90 men were inoculated onto the three mediums Dysentery bacilli were isolated on six occasions with the desoxycholate citrate medium and on three occasions with the Wilson and Blair medium but only negative results were obtained with the MacConkey medium In the second batch, single specimens from 170 men were examined on the desoxycholate citrate and MacConkey mediums Dysentery bacilli were isolated on 24 occasions in each case only on the desoxycholate citrate medium From one case both Flexner and Shiga strains were isolated Both new mediums proved more efficient than the MacConkey

(3) J Roy Army M C rp 80 151 153 M rch 1943

common as bacillary dysentery Hospital stay was longer and time lost greater in amebic dysentery Furthermore mortality from amebiasis was 0 8 per cent with no death occurring from bacillary dysentery in nearly 700 cases

Hepatitis was present in over half the cases of amebic dysentery and liver abscess in 2 8 per cent All grades of severity of the disease were seen from the very acute with extensive ulceration 20–30 stools daily fever and prostration to the mildest of diarrheas with traces of mucus showing occasional vegetative forms and the symptomless type in which cysts of Endamoeba histolytica were found in the feces The commonest type began with diarrhea 5–6 stools daily for three to six days then became more severe with blood and mucus in 8–12 stools daily and malaise anorexia slight fever abdominal colic and varying tenesmus However the clinical picture varies so much that definite diagnosis can be made only on finding amebas in the stools The stools must be fresh and examined within a quarter hour of passing By sigmoidoscopy combined with microscopy of fresh specimens an immediate diagnosis can be made in 80 per cent of cases Injections of emetine with carbarsone orally produced clinical cure in about half the cases The sulfonamides exert a favorable clinical effect but do not eliminate the ameba Inadequate treatment of the initial attack predisposes to the resistant form of the disease Frequent relapses occurred in 28 2 per cent of all cases and 5 per cent became resistant

Chronic Amebiasis in Soldiers R R Bomford[6] points out that with the return of troops from tropical and subtropical countries the incidence of amebiasis will rise therefore methods of diagnosis and therapy should be reviewed Of 112 patients with a provisional diagnosis of dysentery or its sequelae 33 had amebiasis Cases from West Africa predominated however one patient had never left the British Isles and apparently became infected in Northern Ireland Diagnosis was based on

(6) J R y A my M C p 84 79 83 1945

ever there were only a few Sonne carriers in this group In general, Flexner dysentery appears to respond well, clinically and bacteriologically to sulfaguanidine but this is not an indisputable fact because in most cases the clearance tests were unsatisfactory in both numbers and timing

In Sonne dysentery sulfaguanidine and succinylsulfathiazole have only a limited effect Although clinical response to these drugs is good, their value in clearing Bacterium sonnei from the feces is less satisfactory Two persistent carriers continued to excrete the bacteria for over nine months despite repeated courses of both drugs

To control bacillary dysentery two things are needed (1) all outbreaks of the disease must be subjected to thorough bacteriologic investigations, and (2) stringent clearance tests must be satisfied before a patient can be considered free from infection Since routine examination of all returning soldiers is impracticable any carriers involved in an outbreak should be subjected to rigorous tests before being considered free from infection A standard for the clearance tests is necessary Fairbrother recommends that where laboratory facilities are available daily tests be made until at least 12 successive negative results are obtained and where laboratory facilities are poor 12 successive negative reactions be obtained during at least three weeks Tests should not be started until six days after cessation of treatment if sulfonamides have been used Repeated tests must be made on individuals suspected of being carriers because of intermittency of excretion of Bacterium dysenteriae

Amebic Dysentery in Eastern India A M M Payne[5] reports that in two years he saw some 2 000 cases of dysentery in Eastern India 1 000 of which were cases of amebic dysentery Diagnosis was based on finding Endamoeba histolytica in the stools or demonstration of typical ulcers in the intestine There were a few cases of hepatic amebiasis Amebic dysentery was $1\frac{1}{2}$ times as

(5) Lancet 1 206 09 Feb 1 1943

ment of the reported cases emetine hydrochloride was used for two purposes (1) for treatment of hepatitis for which 12 daily injections of 1 gr were given intramuscularly and (2) to control diarrhea in patients with active dysentery before beginning other treatment three to four injections usually being sufficient for this purpose All patients were given a course of emetine bismuth iodide by mouth and chiniofon retention enemas for 12 days followed by stovarsol for 10 days Minimal dosage usually given to men who had not had this treatment previously was 2 gr of emetine bismuth iodide nightly with 300 cc of 2 5 per cent chiniofon every morning as an enema to be retained for at least six hours Maximal dosage given to men in whom this treatment had failed before was 3 gr of emetine bismuth iodide nightly and 300 cc of a 5 per cent chiniofon solution Most patients had six days of the lower dosage followed by six days of the higher Stovarsol was given in doses of 4 gr twice daily

In a few cases treatment failed completely In the others there was noticeable improvement in color and general condition with relief of symptoms during the course and after it Results were better in officers than in troops the difference probably being due to the fact that the former were given efficient treatment earlier Vigorous and efficient treatment in the early stages persisted in until there is laboratory and sigmoidoscopic evidence of cure might prevent development of a state of intractable symptoms physical deterioration and mental hopelessness as was seen in three patients of the series

[When Johnny comes marching home from trop cal and subtropical countr es sold ers with amebias s as well as sundry other diseases will be seen n increasing numbers by doctors more or less unfam liar with tropical d seases Even the larger military establishments are not above occas onal error Recently there came under my observation a young ens gn who had been unsuccessfully t eated for ulcerat ve colitis n a na al hospital over a period of 18 months The frequent bloody d scharges made such d agnosis plaus ble But the feces were found to be swarming with Endamoeba

vegetative amebas in the feces in 6 cases, cysts in the feces in 24, vegetative amebas in scrapings of mucous membrane taken through the sigmoidoscope in 2 and sigmoidoscopic appearances alone in 1 In 14 cases diarrhea was not a recent complaint and had never been a prominent symptom Cases of chronic amebiasis may therefore be missed unless the condition is suspected in patients whose main symptom is something other than diarrhea and unless a routine method, including repeated examinations of stools sigmoidoscopy and examination of specimens taken through the sigmoidoscope, is followed in diagnosis Diagnosis in the reported cases was also suggested by a history of previous dysentery former residence in tropics or subtropics with one or more of the symptoms of diarrhea, abdominal pain and discomfort poor general health slight fever, loss of weight and unsettled stomach, tenderness over the colon or liver and gross appearance of the stools which were occasionally characteristic with blood, mucus and a typical odor, but more often simply watery or unformed

Of 30 patients, 20 had been treated previously for amebiasis and 10 had not Of the 20 7 had received only injections of emetine hydrochloride sometimes on several occasions In almost every case this had produced temporary relief only Only 7 of the 20 had had an efficient course of emetine bismuth iodide and chiniofon retention enemas Others had been treated at different times with emetine stovarsol and a few doses of emetine bismuth iodide or a few enemas sometimes of chiniofon and sometimes of other fluids not usually considered amebicidal

There is general agreement that emetine hydrochloride by injection usually abolishes symptoms but rarely has permanent effects that emetine bismuth iodide or auremetine given orally is the most effective single drug and that simultaneous administration of emetine bismuth iodide or auremetine and chiniofon retention enemas probably gives the most permanent cures In treat

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histolytica and intensive treatment fortunately resulted in gradual but complete recovery —Ed]

Giardiasis with Unusual Findings P B Welch[7] (Miami Fla) reports on 29 cases 13 being seen two years ago and 16 recently Roentgen evidence of functional and anatomic changes in the duodenum, duodenal cap pylorus and prepyloric portion of the stomach, attributable to giardial infestation were observed in 73 per cent of the 29 cases These changes must be considered characteristic of the severe form of the disease

Eosinophilia heretofore not considered characteristic of the disease was observed in 7 of 12 cases in the group of 13 and in 15 of the newer cases In the first group 5 of the 6 patients examined after atabrine therapy showed a return to a normal count and in the second group 11 In children irregularity was observed in the response to atabrine therapy, probably owing to low incidence and mild intensity of abdominal symptoms in these children and to the fact that infestations were found incidentally in the stools during routine check up Thus there was an original total eosinophilia in 22 of 29 cases differential white blood cell counts were made after atabrine therapy in 21 of these and a return to normal was observed in 16 an incidence of response to atabrine therapy of 76 per cent presumptive evidence that the eosinophilia was attributable to the giardial infestation A relatively high white blood cell count 10 000 or over was found in 15 cases with a drop after atabrine therapy in 11

Epidemic Vomiting Sickness (Spencer s Disease) A G Bower[8] (M C U S N R) states that this condition is relatively rare in persons over 40 and commonest in small children Death has not been reported but hospitalization is sometimes needed to combat severe dehydration with attendant acidosis Symptoms vary greatly Adults are less sick than children Recovery is usual after 24–36 hours followed by 2 or 3 days of lassitude anorexia and weakness Chief symptoms are vom

(7) Gastroenterology 3 98 10 August 1944
(8) California & West Med 6 2 3 34 May 1945

iting and/or diarrhea if only one symptom is present it is usually vomiting The disease tends to occur abruptly in one or two members of a family the other members getting it at intervals of 24–48 hours until every one has it except adults who had a previous infection These are either spared or have only abortive attacks lasting a few hours with nausea anorexia and sometimes vomiting Epidemics are occasionally explosive in one community over 500 cases occurred in three days then the epidemic subsided

In children typical symptoms are nausea vomiting abdominal cramps and diarrhea Occasionally there are headache backache chills and low grade fever and rarely a few days of mild acute jaundice Appendicitis has been diagnosed in some cases because of localization of the pain with rebound tenderness on examination at operation the appendix has been found normal except for scarlet hyperemia which is evenly distributed throughout the entire gastro intestinal tract Normal or diminished white blood counts are the rule if they are appreciably raised after adequate hydration some secondary factor is present or diagnosis is questionable Sometimes there are hyperemic tonsils and occasionally there is bronchitis or bradycardia

Despite intensive search the responsible etiologic agent has not been found it probably is a virus The usual bacteria responsible for gastro enteritis have been ruled out

Treatment is symptomatic oral medication is useless because of prompt vomiting Bed rest in a quiet room with dextrose solution by venoclysis is indicated As nausea subsides a few drops of sweetened liquid may be given at frequent intervals and the quantity increased as tolerated If vomiting recurs everything must be done over again Physics are contraindicated as are sulfonamides Milk of bismuth combined with chalk mixture U S P IX has been valuable when patients can sip and retain it Heat to the abdomen is comfortable

The disease is self limited and usually ends in 3 days but may take as long as 10 Differential diagnosis includes other types of acute gastro enteritis, food poisoning and acute conditions of the abdomen, especially acute appendicitis

Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause Hobart A Reimann, John H Hodges and Alison H Price[9] (Jefferson Med College) report on this apparently new" disease which occurred as a widespread mild epidemic characterized by anorexia malaise diarrhea nausea and vomiting in October and November of both 1943 and 1944 in Philadelphia and in other widely scattered places at the same time In a group of medical students studied in 1943 20 per cent had the condition and in 1944 about 10 per cent The outbreaks were similar to epidemics reported from other places in the United States and from Germany Canada, England Denmarl Australia and elsewhere and were probably of the same entity or a similar one They were apparently not related to food or water and were not caused by any known bacilli of the so called enteric group If the cause is a filtrable virus it is not known whether the infection is primarily one of the respiratory tract central nervous system or gastro intestinal tract The last seems most likely The disease could not be transmitted to animals nor could a filtrable agent be isolated However experimental studies still in progress suggest that the disease can be transmitted to volunteers by inhalation of a fine mist of filtered nasopharyngeal washings or stools from patients delivered by Wells flasks and compressed air The infection is thus believed to be air borne and to gain entry through the respiratory or gastro intestinal tract The syndrome may be common and is probably often ignored unrecognized or mistaken for influenza food poisoning bacillary dysentery, acute appendicitis or mesenteric adenitis

The condition is usually so mild that no treatment is

(9) J A M A 127 16 Jn 6 1945

needed Rest in bed and local application of heat give relief for abdominal discomfort Voluntary abstinence from food usually controls nausea In the authors series vomiting spontaneous or induced often lessened epi gastric discomfort or nausea Headache and aching were relieved with aspirin or codeine Only in the severest cases was intravenous administration of 5 per cent glu cose solution needed It caused striking improvement The diet should be restricted according to the patient s desire or tolerance

Iron Deficiency and Anemia Associated with Car cinoma of Proximal Portion of Colon R Lee Clark Marschelle H Power Frank J Heck and Claude F Dixon[1] (Univ of Minnesota) studied 23 patients with carcinoma in some portion of the colon the proximal portion being involved in 21 splenic flexure in 1 and rectosigmoid in 1 The last two patients had anemia and were used for comparison Evaluation of clinical factors disclosed no correlation between any particular factor and the anemia However diarrhea indigestion ano rexia nausea or excessive pain was present separately or combined in nearly all cases and nutritional status was greatly altered average weight loss being 16 3 lb Average age and sex had no relation to anemia Location of the carcinoma appeared to be of statistical impor tance large series of patients indicated that anemia occurred in about 50 per cent of patients whose carcin oma was on the right side and in only about 5 per cent of patients whose carcinoma was in the left half of the colon

Grade of activity of carcinoma cells was inversely pro portional to degree of anemia Thus most profound anemia was associated with a low grade of malignancy A low grade large ulcerating penetrating nonobstruc tive carcinoma was associated with metastasis in about half the cases The largest carcinomas and those existing for the longest period before producing symptoms were

(1) M Cl N rth Ameri a 9 958 97 July 1945

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Epidemic Diarrhea Nausea and Vomiting of Un known Cause Hobart A Reimann John H Hodges and Alison H Price[9] (Jefferson Med College) report on this apparently new' disease which occurred as a wide spread mild epidemic characterized by anorexia malaise diarrhea, nausea and vomiting in October and November of both 1943 and 1944 in Philadelphia and in other widely scattered places at the same time In a group of medical students studied in 1943 20 per cent had the condition and in 1944 about 10 per cent The outbreaks were similar to epidemics reported from other places in the United States and from Germany Canada England, Denmark Australia and elsewhere and were probably of the same entity or a similar one They were appar ently not related to food or water and were not caused by any known bacilli of the so-called enteric group If the cause is a filtrable virus it is not known whether the infection is primarily one of the respiratory tract, cen tral nervous system or gastro-intestinal tract The last seems most likely The disease could not be transmitted to animals nor could a filtrable agent be isolated How ever experimental studies still in progress suggest that the disease can be transmitted to volunteers by inhalation of a fine mist of filtered nasopharyngeal washings or stools from patients delivered by Wells flasks and com pressed air The infection is thus believed to be air borne and to gain entry through the respiratory or gastro intestinal tract The syndrome may be common and is probably often ignored unrecognized or mistaken for influenza food poisoning bacillary dysentery, acute appendicitis or mesenteric adenitis

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(9) J A M A 127 15 Jn 6 1945

of intestinal polyps from the earliest epithelial change to frank carcinoma The earliest recognizable sign is more rapid proliferation of the epithelium at one site than in neighboring epithelial elements Possibly some restraining or inhibiting factor has been removed to permit an indefinite degree of overgrowth Sometimes this change progresses to pedunculation of the mucosa perhaps to afford a greater base and easier nutritional supply for the growing structure When this occurs a pedunculated so called benign polyp is formed When the polyp first begins to develop the epithelium in the glands shows primary hyperplasia The increase in number of cells results in enlargement of each crypt of Lieberkuhn involved in the proliferative process The structure then begins to elongate and limited by muscularis mucosae and subepithelial structures growth proceeds toward the intestinal lumen Such glandular hypertrophy becomes evident in a localized region in which the glands are taller and deeper than neighboring normal structures A tiny plaque or elevation is produced on the mucosal surface of the bowel Other changes follow Thus the tubules often become branched and the nuclei of the cells begin to pile on each other They lose their normal position near the membrana propria and move out toward the lumen of the tubule More cytoplasm appears between nucleus and base of each cell and the outline of the nuclei changes becoming spherical rather than fusiform The chromatin content of the nuclei increases in many cells In others a vesicular character appears and mitotic figures are frequent Individual cells become more cuboid than columnar Cells lose normal alinement and eventually are a heterologous group without regularity of position The outlines of the glands become irregular The cells lose their ability to produce mucus gradually At the site of primary hyperplasia and in the benign polyps the basement membrane is intact Later the cells burst through it and seemingly flow into the glandular interstices When these changes are well estab

situated in that part of the colon in which cancer is most frequently associated with anemia

The type of anemia in patients with cancer in the proximal portion of the colon was the same as that produced by a deficient supply of iron for elaboration of hemoglobin The abnormal demands made on the iron supply of the body were increased when the growth was in the proximal segment while ingestion and absorption of dietary iron appeared to be more retarded than when the growth was in the distal portion of the colon Study of serum iron concentration furnished additional confirmation that a deficiency of iron was present In all cases of cancer of the right half of the colon, serum iron concentration was low If severe anemia was present there was marked decrease in concentration of serum iron The anemia could apparently be arrested, with the cancer in situ following iron therapy, if the iron was of sufficient amount and was absorbed

In all cases following resection of the cancerous segment of bowel, elevation of hemoglobin values was accompanied by a return of concentration of serum iron to more nearly normal regardless of source either dietary or medicinal of the absorbed iron The definite impression is obtained that iron therapy accelerates recovery from anemia and that the more marked the hypochromic anemia the greater the need for iron The confusing variable is that related to absorption and this perhaps can only be eliminated when a suitable preparation of iron for parenteral administration is available In five cases resection was done by exteriorization thus isolating the colon from regions of absorption during the period of recovery from the anemia This did not prevent absorption of iron needed for elaboration of hemoglobin

Pathogenesis of Intestinal Polyps John S Atwater and J Arnold Bargen (Mayo Clinic) in a series of autopsy specimens were able to trace the pathogenesis

( ) Gastroenterology 4 395 408 May 194

absorption in intestinal infections in which the infecting organism is not found in the blood stream it was note worthy that in these three series of patients and another series treated with sulfapyridine the efficacy of the drug particularly in clearing up carriers was in direct pro portion to the degree of its absorption from the intestine

Sulfathalidine in Intestinal Disease J A Bargen[4] points out that for treatment of intestinal diseases a drug should be in contact with the intestinal wall for a continuous period with minimal systemic absorption Since the intestinal tube is large large quantities of the drug are needed To fulfil these criteria such drugs as azosulfamide (neoprontosil) sulfaguanidine sulfasuxi dine and sulfathalidine were developed and found effec tive in various intestinal disorders Most other sulfon amides were absorbed in too large amounts when given in effective doses and thereby caused too great toxic symptoms to be of use in intestinal diseases

Sulfathalidine was used as part of treatment of ulcera tive colitis of the streptococcic variety in 37 patients Some had received one or all of the other three drugs A number had a sensitivity to neoprontosil manifested by erythematous rash sore throat chills and fever With discontinuation of the drug symptoms subsided prompt ly When the drug was changed to sulfathalidine only minor reactions occurred in a few patients One pa tient a woman 47 had similar reactions to sulfathia zole sulfasuxidine neoprontosil and sulfathalidine Another a woman 55 had a severe reaction to sulfa suxidine with fever generalized erythematous rash and general malaise and a mild similar reaction to sulfa thalidine Generally when one of the other drugs caused a reaction sulfathalidine did not Many patients had shown an initial satisfactory response to one of the other three drugs but this response was not sustained With sulfathalidine response was sustained

Response to sulfathalidine was good in 26 patients

(4) P Staff M t M y Cl n 0 85 87 M 1 1945

lished the muscularis mucosae no longer serves as barrier, the cells spread freely into the subepithelial tissues and glandular structures may or may not be retained. Minimal changes are noted in the mucosal stroma until the larger polyps have been formed. Then the polyps are frequently the seat of inflammatory changes and small hemorrhage. Necrosis may be present inside the polyps.

Polyps including tiny sessile lesions, were found in 69 per cent of 241 colons studied. There was no difference in occurrence of polyps in the two sexes. Mean average age of patients harboring polyps was 64 years.

Lymphoid structures seem to play only a casual role in pathogenesis of intestinal polyps. The term "benign polyp" should not give the idea of an innocent tumor but rather of one stage in pathogenesis of a carcinoma which eventually will definitely develop.

Sulfanilylbenzamide, Sulfanilylamidobenzamide and Succinylsulfathiazole in Chemotherapy of Sonne Dysentery. R. Swyer and R. K. W. Yang[3] report on 179 patients with bacteriologically proved Sonne dysentery treated with these sulfonamides in doses governed by body weight. The stool became formed, normal in color and free from blood or mucus in 24–48 hours in the sulfanilylbenzamide treated series and in 38 of these cases bacteriologic clearance was obtained in an average of 1.8 days. Improvement in characteristics of stools was marked with sulfanilylamidobenzamide, but rather less so than with sulfanilylbenzamide. The average time for clearance was 3.6 and 2.5 days with full and half doses respectively. With succinylsulfathiazole (sulfasuxidine) there was no great improvement in stools but clearance time was 2.4 days. Bacteriologic relapse rates were with sulfanilylbenzamide 7.3 per cent, with sulfanilylamidobenzamide, full dose 15 per cent and half dose 3.3 per cent, and with succinylsulfathiazole 34.6 per cent.

Although preference is given drugs of a low degree of

(3) Brit. M. J. 1: 149-151, Feb. 3, 1945.

DISEASES OF METABOLISM AND NUTRITION

Diabetes Mellitus As Observed in 100 Cases for 10 or More Years General observations by Russell Richardson and Morris A Bowie[5] (Univ of Pennsylvania) on 100 patients controlled by insulin and measured diets (high carbohydrate low fat) for 10 or more years show that diabetes does not always increase in severity After comparing diet and insulin at the beginning and end of a five year period it was found that the diabetes of 45 per cent of the patients had not advanced Ten of these patients required less insulin at the end than at the beginning Of the 55 who needed more insulin some had also received increases in diet Acidosis occurred in three patients during the past 10 years Arteriosclerosis was present in some patients but none had amputations Mild anemia was found in 26 patients only 3 had less than 4 000 000 red cells and less than 13 5 Gm of hemoglobin per 100 mg blood Chronic or repeated acute infections were present in 39 patients with cholecystitis (16 cases) pyelonephritis (9 cases) and tuberculosis (9 cases) the most frequent

Joseph Edeiken[6] (Univ of Pennsylvania) reports the cardiac studies on this group of patients 69 of whom were over 50 and 31 under 50 Hypertension (systolic blood pressure 160 mm Hg) was present in 38 all over age 50 Incidence increased with each decade and was twice as common in women as in men It apparently was not dependent on duration control or severity of the diabetes Ten of the hypertensives had cardiac enlargement, 4 doubtful enlargement and 24 hearts of normal size This incidence of cardiac enlargement is about one half that found in nondiabetic hypertensives Greatest

(5) Am J M S 209 1 8 J u ry 1945
(6) Ib d pp 8 16

fair in 1 slight in 1 and nil in 9 By response is meant reduction in bowel motion, decrease or disappearance of blood from the stools and relief from concomitant symptoms of toxemia The disease was severe in 25 cases, insidious in 10 and fulminating in 2 In one fulminating case response was good and in the other nil Most patients with severe symptoms improved clinically during administration of the drug

In an additional case of regional ulcerative colitis response to sulfathalidine was very good In two of three cases of regional ileitis there was marked improvement in intestinal *symptoms and general conditions*, in the third there was slight improvement

Rather large amounts of sulfasuxidine have been given routinely for the past two years to patients for whom *intestinal resection has been planned The drug* was given several days before operation Occasionally rather severe toxic symptoms occurred In a few cases sulfathalidine was given without such toxic symptoms or with minimal symptoms

Thus sulfathalidine seems to have advantages over the other drugs when used for intestinal conditions It is less toxic and frequently produces improvement not obtained or sustained with the others and smaller amounts are usually more effective

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ficial hemorrhages can be expected with increased duration of diabetes even under closely observed therapy

Meyer Naide[8] (Univ of Pennsylvania) examined peripheral vascular findings in 89 of the 100 patients Three of the patients under 50 and 30 of those over 50 had evidence of peripheral arteriosclerosis Premature arteriosclerosis was therefore not common Severity of diabetes did not affect the incidence Adequately controlled patients had a smaller incidence of arterial disease Arteriosclerotic occlusive disease appeared in 42 per cent of the women as compared with 23 per cent of the men. Neuritis was present in 31 of the 89 patients chiefly in those with arteriosclerosis

Cause of Death in Diabetes Stanley L Robbins and Arthur W Tucker Jr[9] (Boston City Hosp) studied causes of death as revealed by autopsy in 307 diabetics from 1932 to 1942 and in about 2 800 nondiabetics during 1936 1937 1941 and 1942 These years were selected so as to include the pre and postsulfonamide eras and changing therapies Adequate histologic material available in 268 of the diabetic cases was reviewed to evaluate the frequency of histopathologic changes in diabetes

Distribution of the causes of death in the two groups is presented in Table 1 Peripheral vascular disease indicates cases of vascular insufficiency leading to gangrene and death with or without infections Pulmonary infections include a wide variety of inflammatory diseases of the lungs such as bronchiectasis lung abscess pneumonia and tuberculosis Unknown causes of death traumatic deaths anemias and various less frequent fatal diseases are grouped under other causes

The most frequent cause of death in the diabetic group was pulmonary infection cardiac decompensation and coronary occlusion follow In the controls pulmonary infection also was first with carcinoma second and cardiac decompensation third

(8) Am. J M Sc 09 3 8 J ry 1945
(9) New Engl d J Med 31 865 868 D 8 1944

cardiac enlargement was found in patients with electrocardiographic evidence of myocardial abnormality (with or without hypertension) and conversely, there was a low incidence of electrocardiographic changes indicative of myocardial abnormality in the hypertensives without cardiac enlargement Evidence of left ventricular hypertrophy or left ventricular strain was not observed in any patient with hypertension Only three patients under 50 had abnormalities of the heart which could be attributed to the diabetes these three were aged 24 30 and 47 and had diabetes for 15 16 and 15 years The low incidence of cardiovascular abnormalities in the younger group when compared with the incidence in other series of diabetics on a high fat–low carbohydrate diet, is suggestive evidence of the value of the high carbohydrate, low fat diet in reducing the incidence of premature cardiovascular abnormalities

Irving H Leopold[7] (Univ of Pennsylvania) studied ocular findings in the same 100 patients and compared them with those previously reported by Waite and Beetham in nondiabetics and diabetics with disease and treatment of varying duration Closely controlled therapy apparently reduces incidence of corneal wrinkles in diabetics Increased motility of pigment is not affected by this therapy and there is no significant difference in incidence of iritis muscle palsies optic neuritis optic atrophy or the senile type of lens changes in treated diabetics and in nondiabetics Complicated cataracts were more rare in diabetics treated over 10 years but subcapsular snow flake cataracts were still found Incidence of sclerosis was similar in all groups Deep retinal hemorrhages and exudates increase with duration of diabetes and may be slightly decreased by closely observed therapy Although arteriosclerosis hypertension renal disease sepsis and hyperglycemia may influence the incidence of deep punctate hemorrhages and waxy exudates none of them is the basic etiologic factor Increased super

(7) Am J M Sc 09 16 3 Janu ry 1945

[Statistical analyses based on anatomic studies admittedly give more accurate *information regarding causes* of death than do analyses based solely on clinical observations Some statisticians might advance the criticism that the number of cases studied (_07) might be too small to warrant definitive conclusions That the deaths from pulmonary disorders exceeded those from cardiovascular diseases is rather illuminating —Ed.]

Hyperinsulinism Solon S Bernstein[1] finds that despite growing recognition of this disease the term hyperinsulinism is still often loosely applied to any form of

TABLE 2—HISTOLOGIC CHANGES IN ?68 DIABETICS

LESION	++++	+++	++	+	NONE	SIGNIFICANT CHANGE %
Kidneys						
Glycogen nephrosis	1?	44	4?	14	9	42
Benign nephrosclerosis	9	50	58	19	93	55
Intercapillary glomerulosclerosis	7	3	21	?	01	?0
Pancreas						
Hyalinization or fibrosis of islets	8	24	34	1?	106	36
Liver						
Nuclear glycogen	27	54	60	20	53	66
Fat	13	?2	34	30	41	48

hypoglycemia whether of hormonal hepatogenic central nervous system or functional origin. Whipple's classic triad defining the bases for accurate diagnosis of islet cell adenoma should be applied to every case These criteria are unusually low postabsorptive (fasting) blood sugar level 50 mg per cent or less symptomatic attacks of extreme hypoglycemia with signs of central nervous system disorder vasomotor or psychic with in some cases coma or convulsions dramatic and immediate recovery following administration of glucose orally or by vein When these criteria are present and pituitary,

(1) J Mt S i H sp 1 66 78 M y-Ju e, 1945

Table 2 indicates the frequency of certain histopathologic changes in the diabetic group These lesions were arbitrarily designated as + to ++++, only changes of ++ or greater being considered significant Evidence

TABLE 1 —CAUSE OF DEATH

CAUSE OF DEATH	DIABETIC GROUP			NON DIABETIC GROUP %
	Cases	%	Corrected %*	
Coma	22	7 2	—	—
Vascular disease				
Cardiac decompensation	35	11 4	12.3	1?6
Coronary occlusion	31	10 0	10 8†	4.3†
Cerebral hemorrhage and thrombosis	15	4 9	5.2	7.5
Peripheral vascular disease	13	4.2	4 5†	.0†
Central (pulmonary embolism)	7	2.3	2 4	2 8
Renal disease				
Glomerulonephritis	2	0 7	0 7	0 4
Acute pyelonephritis	21	6 8	7 3†	1 8†
Miscellaneous	2	0 7	0 7	2 0
Infection				
Pulmonary	73	23 8	25 6	24.2
Peritoneal	13	4 2	4 5	4.8
Extremities	7	2.3	2 4†	0.5†
Other infections	23	7.2	7 7	5.9
Cancer	24	7 8	8 4†	14 7†
Other causes	20	6 5	7 0	17 0

* From a statist cal v wpoint, to compa e the diabet c a d control groups it is ne essary to elim nate coma as a, s nce oma is a h ard p c l ar only to the diabetic and not found in the control group This column, therefore represents the diabeti seri s from wh ch c ma cases have been ex cluded the mortality percentage be ng rec mputed to be strictly comparable with those f the control gr up

† Statistically signific nt diff rences

of cirrhosis was found in 27 of the 268 cases alcoholic cirrhosis in 13, biliary cirrhosis in 11 and healed acute yellow atrophy in 3

Average age of the diabetics at death was not significantly different from that of the nondiabetics being 59 6 years for the diabetics and 59 8 years for the nondiabetics

of the head of the pancreas and not removed even after subtotal dissection Persistence of hypoglycemic symp toms after removal of an adenoma or partial pancreatec tomy indicates need for a second operation Existence of hyperinsulinism in presence of hyperplastic and hyper functioning islet cells without an adenoma is seriously questioned Recent histologic studies suggest that the hyperplastic zones actually represent multiple frequent ly microscopic adenomatosis

The usual morphologic evidences of malignancy are invalid as an index of malignancy in islet cell adenomas and the outlook for complete cure after resection of the tumor is excellent The sole positive criterion of malig nancy is presence of metastasis usually lymphatic or hepatic Glucose tolerance curves in hyperinsulinism are frequently ambiguous and have not proved to be of sig nificance diagnostically The symptomatic relief often obtained with high carbohydrate high fat frequent feed ing regimens lulls both physician and patient into false security and obscures the inexorable course with both an increase in the operative risk and a lessening of the chance for complete cure

Simple Modification of Colorimetric Method for Rou tine Thiamine Clearance Tests Melvin Hochberg and Daniel Melnick (Long Island City N Y) report a simple and rapid modification of the Melnick Field col orimetric method By testing a one hour urine sample the benzyl alcohol extraction step for quantitative and selective removal of thiamine from the concentrated urine is eliminated The method consists of direct adsorp tion of the vitamin from the one hour urine sample on a simplified zeolite column its elution and coupling with diazotized p amino acetophenone and finally extraction and measurement of the pigment formed Results ob tained with this method compare favorably with those obtained with the original procedure (see Table) Twelve

(2) J B l Ch m 156 53 59 N mb 1944

adrenal thyroid, thalamic and hepatic diseases have been ruled out presence of an islet cell adenoma must be assumed and operation done without delay, as metastases may develop and in some cases irreparable cerebral damage with mental deterioration due to prolonged hypoglycemia Operative results are almost uniformly spectacular

The nervous and emotional derangements frequently identified with hyperinsulinism have led to many false diagnoses Personality and behavior alterations are frequent in presence of an islet cell adenoma and may run the gamut of psychologic symptomatology Transient or prolonged periods of apathy loss of zest amnesia and fatigue may alternate with more acute attacks of tremulousness weariness vertigo and sweating Himwich and his co workers divide the psychologic characteristics of hypoglycemia into five progressive phases and ascribe this sequence to variable metabolic rates throughout the brain The cortical phase is indicated by sweating muscular relaxation salivation tremors and gradual clouding of consciousness In the second or subcorticodiencephalic phase motor restlessness and primitive movements appear The mesencephalic or third phase is characterized by tonic spasm and often a positive Babinski sign A premyencephalic phase follows with tonic episodes chiefly extensor simulating that of Sherrington s decerebrate dog In the fifth or myelencephalic phase there is deep coma The occurrence of such disorders as a manifestation of hypoglycemia suggests the need for routine blood sugar determinations in all unexplained psychoneurotic and psychotic states

Since islet cell adenomas are frequently multiple, adequate exposure with careful inspection and palpation of the entire pancreas is necessary Failure to find an adenoma justifies either subtotal or as recently successfully done total pancreatectomy Most operative failures are due to an overlooked adenoma deep in the substance

lesions around the nose cheilosis angular stomatitis ocular manifestations such as burning and itching photophobia, impaired visual acuity and corneal vascularization sensory neurologic disturbances, chiefly a sense of muscular weakness in co ordination ataxia and paresthesia without real loss of power or sensation or

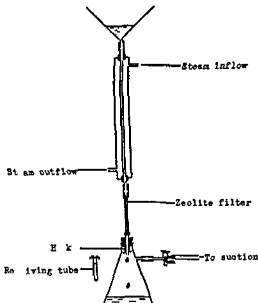


FIG 111—Appa tu f adsorpt n d lut n of th min in uri (H hb g Mein k, p 717)

muscular wasting associated with loss of visual and auditory acuity

This syndrome includes much more than that called ariboflavinosis Stannus believes any differences are a question of comparative intensity and duration of the underlying pathogenic process He attributes the whole syndrome to riboflavin deficiency a hyporiboflavinosis but is uncertain whether any other factor in the B_2 complex plays a part

to 15 samples of urine can be analyzed by a single ana lyst in eight hours of working time, using only apparatus usually available in a routine clinical laboratory

APPARATUS —A glass funnel is connected to a condenser by a short piece of rubber tubing (Fig 111) The latter is similarly joined to a tube having an internal diameter of 8 mm for a length of 4½ in. followed by a constricted portion about 4 mm. in diam

COMPARISON OF RESULTS OBTAINED BY ORIGINAL AND BY SIMPLIFIED COLORIMETRIC PROCEDURE

SUBJECT	RANGE OF URINARY THIAMINE	TOTAL THIAMINE EXCRETION AFTER TEST DOSE			
		Oral		Intramuscular†	
		Simple Method	Original Method	Simple Method	Original Method
1	Normal	980	830	110	90
2	Normal	1 630	1 4[illegible]0	100	160
3	Normal	1 080	1 070	1[illegible]0	100
4	Normal	1 6[illegible]0	1 460	140	1[illegible]0
5	Normal	1 [illegible]60	1 [illegible]00		
6	Deficient	110	1[illegible]0	25	22
7	Deficient	180	2[illegible]0	28	37
8	Deficient	260	230	32	38
9	Deficient	180	190	37	30
10	Deficient	200	210	43	37

Five mg of thiamin was taken orally after a large mid-day meal, and urine was collected during the subsequent 4 hours Values are expressed in gamma per 24 hours

† Thiamine 0 35 mg per sq M body area, was injected intramuscularly 1 hour after the last meal, and the subsequent 4 hour urine samples were collected from the fasting subjects Values are expressed in gammas per four hours

eter A plug of glass wool is placed at the top of the constriction and exactly 3 Gm of the treated zeolite is added to the tube If there is no laboratory steam line a 1 L flask of boiling water equipped with a two way stopcock may be used

Some Problems in Riboflavin and Allied Deficiencies Hugh S Stannus[3] distinguishes between pellagra and a group of symptoms occurring as a more or less com plete syndrome apart from symptoms generally attrib uted to nicotinic acid deficiency The syndrome consists of mild constitutional symptoms such as mental and physical fatigue and symptoms referable to heart and gastro intestinal tract skin manifestations such as mild erythema and pruritus of scrotum and vulva, seborrheic

(3) Brit M J 103 105 July 140 144 July 9 1944

given for 12 weeks The boys remained in excellent health throughout The amount of riboflavin excreted in the urine was about twice the riboflavin intake while that in the feces was about five to six times the intake This suggests that riboflavin is synthesized by intestinal bacteria Succinylsulfathiazole was given in an attempt to inhibit synthesis of riboflavin as it is known that this drug inhibits the bacterial synthesis of thiamine in the human intestinal tract Thiamine almost disappeared from the stools but the amount of riboflavin was not decreased actually daily output was a little higher after ingestion of the drug Reduction of urine output occurred temporarily in two boys and in one other who had previously been excreting quantities of riboflavin greater than the rest there was reduction to the levels of the other subjects

The authors do not doubt that riboflavin deficiency may occur but these results suggest that riboflavin may not be a dietary essential under all conditions

Experimental Studies on Man with Restricted Intake of B Vitamins are reported by Ancel Keys Austin Henschel Henry Longstreet Taylor Olaf Mickelson and Josef Brozek[5] (Univ of Minnesota) The basal diet on which the subjects existed for 161 days consisted of an average of 0 185 mg thiamine 0 287 mg riboflavin and 3 71 mg niacin per 1 000 calories with other factors of the B complex more or less in proportion the diet provided an average of 3 300 calories daily All subjects were studied in an extended preliminary standardization and control period and the terminal control consisted of a 33 day experiment with a synthetic diet providing substantially no vitamins of the B complex

Of eight normal young men given the controlled dietary four (supplemented group) also received 1 mg thiamine 1 mg riboflavin and 10 mg niacinamide daily All men remained in the laboratory for the experimental period of 161 days The 24 hour urinary excretion of

(5) Am J Phy l 144 5 4 J 1945

All symptoms respond to treatment with yeast It is suggested that the assumption is warranted that cells forming the capillary endothelium require all elements needed by other body cells for normal metabolism i e sugar oxygen etc including riboflavin Also, the first tissue to suffer effects of riboflavin deficiency may be the endothelium of the capillary system with the initial result a reversible functional disturbance of the capillaries—a capillary dysergia —manifested by dilatation and impaired flow There is in turn interference with normal cellular metabolism and consequently a derangement of tissue function by disturbance in the milieu interieur with such derangement relatively greatest in tissues with highest degree of capillarity and greatest metabolism As long as the functional disorder is not too intense and does not persist too long, recovery may occur, otherwise irreversible processes lead to pathologic changes This hypothesis appears to explain the incidence of symptoms and distribution of signs in riboflavin deficiency Interference with tissue cell metabolism is probably of the nature of an anoxia in its wide sense

Stannus suggests that disorders of capillary function— dysergia quite apart from affections of the rest of the vascular system may play a much more important part than commonly supposed in pathogenesis of many conditions including pellagra due to nicotinic acid deficiency and probably also fibrositic rheumatism some psychoses and neuropathies

Biosynthesis of Riboflavin in Man Victor A Najjar George A Johns George C Medlury Gertrude Fleischmann and L Emmett Holt Jr[4] (Johns Hopkins Univ) studied 12 boys aged 10–16 given an experimental diet of vitamin free casein crisco dextrimaltose a mineral mixture and a vitamin mixture which contained no riboflavin Assay for riboflavin showed appreciable quantities in only the casein which provided a daily riboflavin intake of between 70 and 90 micrograms This diet was

(4) J A M A 1 6 357 358 Oct 1944

sisted for six months on an adequate intake of all nutri ents except B vitamins which had been restricted, the other two had received the same diet plus adequate sup plements of the B vitamins Accordingly there were two men in each of four groups with reference to previous and present diets restricted deficient control deficient restricted control and control control

Anorexia and later nausea and vomiting began in the restricted deficient men after about eight days and pro gressed to almost complete inability to eat in 18–20 days the control deficient men showed the same changes with a lag of 5 or 6 days After 23 days the men in both of these groups were given daily supplements of thiamine only with a rapid return of appetite and regression of other symptoms and functional abnormalities The 24 hour urinary excretion of thiamine fell to the vanishing point in two to four days in all the deficient men excre tion of riboflavin also fell abruptly but tended to stabil ize in a week at levels considerably in excess of intake Excretion of F showed no marked relation to intake of niacin in any of the men Changes in blood chemistry in the deficient men were primarily increases in both lactic and pyruvic acids in rest in work and after glucose ingestion These changes were insignificant up until two weeks and even thereafter were slight Gastric emptying and tests of liver function showed no significant changes Basal metabolism was substantially constant The re stricted deficient men showed progressive and eventually marked deterioration in endurance co ordination and fitness with trifling or no effects on strength vision hear ing and speed Similar results were obtained with the control deficient men with a lag of about one week Sim ple muscle efficiency was unaltered but cardiovascular capacity and respiratory efficiency were reduced There was diminution in heart size but no important electro-cardiographic alterations All deficient men showed pro nounced tachycardia in work but only one developed resting bradycardia Intellective functions were resistant

thiamine became substantially constant in less than one month in both restricted and supplemented groups The 24 hour urinary excretion of riboflavin became substantially constant in about two months in the restricted group In the supplemented group there was no tendency toward progressive alteration from the beginning For the last three weeks of the experiment daily urinary excretion of riboflavin averaged 137 and 438 μg in the two groups No differential changes were noted in either group in pulse rate during and after endurance and brief exhausting work, Harvard physical fitness test scores strength, psychomotor functions heart size electrocardiograms gastric emptying basal metabolism glucose tolerance, blood lactate in rest and after standard work or glucose ingestion sensory and intellective functions and various objective personality evaluations All clinical, ophthalmic and neuropsychiatric examinations were also negative Resting level of pyruvic acid in the four subjects on low vitamin intake increased from an average of 1 01 mg per 100 ml blood at the beginning of the experiment to 1 15 mg at the end, a statistically significant change There was a slight tendency toward a similar difference in the two groups after brief exhausting exercise No differential change in blood pyruvate followed ingestion of glucose There it is concluded that within the limits of the experiment, vitamin restriction was without significant effect on fitness health and personalities but that the thiamine intake was on the borderline of inadequacy, as shown by blood pyruvate There were no signs of deleterious effects from restriction of riboflavin and niacin

In the second experiment, the young men subsisted for 33 days on a diet adequate except in B vitamins which were limited to 0 008 mg thiamine 0 013 mg riboflavin and 0 1 mg riboflavin per 1,000 calories Four men daily received capsules which provided adequate B vitamins, the other four received placebos Activity was set at 4 000 calories daily Two of the men in each group had sub

patient voluntarily reduced her food intake to lose weight. Pseudohallucinations, smothering spells, nervousness and palpitation developed. Repeated injections of sterile saline solution gave no relief but all symptoms disappeared after administration of thiamine hydrochloride. Laboratory findings were suggestive of diminished cerebral metabolism explaining some of the symptoms. In Case 6 the patient became psychotic; she fortunately had a small unilateral skin lesion on the side of her neck which could be diagnosed as pellagra. She was given niacinamide and changed overnight from an irrational person to one quiet and co-operative and eventually was able to return to work. The patient in Case 9 had been on an inadequate and unbalanced diet for an indefinite period and had nervousness, pseudohallucinations and severe burning of the feet. Three separate injections of saline solution intravenously did not give relief but 100 mg. thiamine hydrochloride relieved her within an hour. The patient in Case 10 was stuporous when hospitalized. She had an enlarged heart, cardiac murmurs, tachycardia, anasarca and a sore and tender liver. There was no response to digitalis. Her "beriberi" heart was treated with intravenous injections of thiamine hydrochloride with excellent results.

There are four essentials for therapy of severe atypical deficiency disease. The diet should contain 4,000 calories and 120–150 Gm. protein and be rich in vitamins and minerals. Basic therapy should include oral administration of ascorbic acid and thiamine, riboflavin and niacinamide. Additional medication should consist of synthetic vitamins as indicated, given either orally or parenterally. Natural vitamin B complex in the form of brewers yeast or extract or rice bran extract and/or liver extract should be given orally or parenterally.

Relationship between Clinical Picture of Mild or Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels. Julian M. Ruffin, David Cayer and William A. Perlzweig[7] (Duke Univ.) report a study

(7) Gastroenterology 3: 340-356, November 1944.

to the deficiency but there were marked changes in personality toward apathy depression and hypochondriasis Detailed clinical ophthalmologic and neurologic examinations were largely negative except for minor indications of neuropathy in the legs The control subjects showed a satisfactory constancy for all variables and functions tested

Thiamine was much the most important B vitamin in this acute restriction Bodily stores of thiamine under these conditions are effective for a few weeks at most The experiment confirmed the conclusion that the restricted diet given in the first experiment was less than adequate or optimum at least in thiamine but that such inadequacy represented only a loss of a few days in the margin of safety

Detection and Treatment of Severe Atypical Deficiency Diease Tom D Spies Robert C Cogswell and Carl Vilter[6] (Univ of Cincinnati) discuss a number of cases of deficiency disease in patients without classic symptoms or definite criteria to illustrate difficulties in diagnosis and therapy of atypical deficiency disease Thorough study was required in all before diagnosis was possible

In Case 1 severe infection followed by greatly reduced food intake led to nutritive failure in an infant aged 5 months He had diarrhea and ulcerated areas on the tongue Administration of 50 mg niacinamide was followed by prompt cessation of diarrhea healing of glossitis and return of appetite In Case 2 an extremely unbalanced diet led to a psychosis which was quickly relieved by judicious nutritive therapy In Case 3 severe sensory symptoms arising from the peripheral nerves of legs and feet were promptly relieved by thiamine hydrochloride, with disappearance of these symptoms the patient was no longer nervous or depressed In Case 4 there was a severe unilateral ocular lesion associated with loss of weight and strength Treatment with riboflavin was followed by healing and good health In Case 5 the

(6) J A M A 1 6 75 759 N v 18 1944

in the 24 hour collection With administration of ascorb c acid capillary resistance began to fall at the period of saturation the level of capillary resistance was lower than at any other time during observat on The Hess test however was not positive even when the negative pressure method re ealed a relatively low capillary resist ance on March " After saturation the dose of ascorbic acid was re duced to 100 mg daily Capillary res stance returned to a higher le el where it apparently was maintained for 1° days until the daily do e of ascorbic acid was ncreased to 500 mg Capillary re sistance then showed a decreas in all three standard areas similar in degree and kind to that obser ed during the process of saturation

Finally the patient was given tablets a day of a preparation from rose hips equivalent to about "0 mg ascorbic acid and 550 provisional units of v tamin P An immediate increase in capillary resistance in each of the three standard areas followed and was maintained for another 10 days during admin stration of the tablets

The observations in Scarborough s two cases are in consistent with the view that ascorbic acid increases capillary resistance Hesperidin (given in Case 2) and a preparation from rose hips rapidly increased capillary resistance with ascorbic acid therapy the latter prepa ration being apparently the more active weight for weight in the ratio of at least 2 7 It appeared that min imal daily requirement for vitamin P to maintain cap illary resistance at a high level is certainly under 550 provisional units and probably under 300

[Granting that the author s observat on is correct this is another good argument fo supplying the essential element as t occurs in nature (c trus fru ts rose hips etc) rather than plac ng too much dependence on a synthetic vitamin concentrate —Ed]

Observations on Undernourished Persons K Perakis and D Bakalos[9] (Athens) report on four types of hun ger edema The cachectic type was characterized by ema ciation and by slight swelling of the face and extremities Extreme weakness was the chief complaint and sudden death occurred regularly in absence of prodromal signs or after diarrhea of short duration Generalized dropsy the second type occurred in less debilitated persons Re covery was usual when there were no intestinal disorders and prognosis was most favorable in younger patients Incidence of the third the polyserositic type was high

(9) D ts h m d W hnsch 69 46 O t 9 1943

of 26 patients classified clinically as having a B complex deficiency, glossitis papillary atrophy of the tongue, cheilosis and peripheral neuritis being considered the earliest and most reliable evidence In all, levels of nicotinic acid, thiamine and riboflavin were significantly lower than those found in a group of normal controls Plasma levels of vitamin A and carotene were also lower than in the normal group Laboratory data therefore indicated existence of multiple deficiencies among patients with physical signs of deficiency of the B complex and suggested that laboratory determinations of vitamin levels are important in recognition of mild or early vitamin deficiencies

Vitamin P Observations on Capillary Resistance in Two Cases of Scurvy Harold Scarborough[8] (Royal Infirm) reports observations made for 60 and 52 days, respectively The first case is given here

Man 46 who lived mainly on bread tinned milk tea, canned and preserved meat margarine and jam complained of weakness lassitude undue fatigue and rheumatics all over the body of three months duration He had dyspnea on exertion slight edema of the right foot and ankle and swollen and bleeding gums. Subcutaneous bleeding had been present for one week Four large ecchymoses were on the legs and there was perifollicular keratosis on the legs thigh and upper arms The right eye had a subconjunctival hemorrhage Extreme tenderness of calves and thigh muscles was present Temperature was 99 F pulse 92 and blood pressure 1_8/69 Urea nitrogen was 18 mg per 100 ml and plasma ascorbic acid about 0 08 mg Red blood cell count was 4 44 with hemoglobin 1? 4 Gm per 100 ml Reticulocyte count was 1 8 per cent White blood cells numbered 4 600 without immature cells and thrombocytes 350 000 Bleeding time was five minutes coagulation tim eight minutes Mean corpuscular volume was 91 μ Clot retraction was 58 per cent and extracorpuscular clot volume 2 per cent Capillary resistance tests gave 400 450 and 500 and the Hess test was negative

He was given a standard diet which contained sources of vitamins A D and B complex but was relatively low in ascorbic acid and probably vitamin P also Further bleeding developed during observation followed by immediate increase in capillary resistance Ascorbic acid 500 mg daily orally was then given and continued until saturation was achieved i e an excretion of ascorbic acid exceeding 5 mg per 100 ml urine and/or a total amount greater than 50 mg

(8) Ed bu gh M J 51 381 38 Septemb 1944

by which amino acids are obtained by digestion of protein are classified into enzymatic and acid hydrolysis procedures The enzymatic procedure has been more extensively used and has given satisfactory results Successful results were also obtained with a protein digest prepared by pancreatic hydrolysis of casein the product containing the amino acids of casein and pancreatic tissue Biologic tests have shown that this material contains all essential amino acids in sufficient concentration to support growth in rats when given as the sole source of nitrogen one of the most rigid tests of efficiency of protein

Use of amino acids is generally indicated when there is failure in normal ingestion digestion and absorption of food protein Hypoproteinemia is an objective evidence of protein deficiency particularly when there is fall in albumin fraction Although often masked by dehydration and increase in globulin fraction a fall in plasma proteins has been observed frequently especially after operations Clinical use of amino acids is specifically indicated when a patient is unable to ingest protein because of severe gastro intestinal disease or persistent vomiting from any other cause In these cases the amino acids are given parenterally This category includes patients with intestinal obstruction local or general peritonitis acute cholecystitis severe peptic ulcer with pain on eating and such chronic diseases as gastro intestinal carcinoma or patients who have undergone abdominal surgery and in whom gastro intestinal rest is needed for healing Patients with advanced inanition are also included in this group Another group includes persons able to ingest protein but in inadequate amounts or with insufficient digestion or absorption in such cases the amino acids can often be given orally but in some parenteral administration may be required The third group includes patients with allergy and intractable especially bleeding peptic ulcers Administration of amino acids by mouth is desirable in many cases and may

Prolonged ascites was frequent but recovery was usual although reaccumulation of fluid occurred after evacuation The serous fluid was deficient in albumin 2 25–5 5 per cent In two cases there was chyle associated with fatty globules Prognosis was less favorable if all serous cavities were involved The fourth type consisted of localized edema of the face and extremities A mild clinical course was characteristic Gastro intestinal disorders played an important role Dilatation of the stomach was frequent with hypo acidity of the gastric juice Diarrhea with 10–30 movements daily was an unfavorable symptom Stools containing undigested food mucus blood and pus were observed in the grave cases in which extensive ulceration of the mucous membrane of the colon was found at autopsy Polyuria and excessive excretion of sodium chloride bradycardia and hypotension were common Capillary alterations in cachectic patients resulted in formation of a vascular nevus on the back of the hand and on the face Frost bite caused by cold alone has not been seen in Athens before but did result from the combined effect of cold and undernourishment Nervous disorders with loss of tendon reflexes and of vesical and rectal control were frequent Epithelial and subepithelial polymorphous keratitis was also frequent

[These observations on the famished victims of war torn countries are of great interest to students of nutrition Of equal interest are the emergency scientific methods of treatment to save useful lives which in former times would have been lost The science of nutrition has made enormous strides —Ed]

Practical Use of Amino Acids in Protein Nutrition Robert Elman[1] (St Louis) discusses the physiologic chemistry of amino acids and points out their value in therapy of impairments of digestion and absorption Administration of amino acids instead of food protein provides protein nourishment in its simplest form and by parenteral administration protein starvation can be avoided Even if the patient requires parenteral fluids these need not be confined to salts or glucose protein building substances can now be supplied easily Methods

(1) J A M A 1 8 659 664 J 30 1945

least 1 L should contain 5 per cent protein digest and 5 per cent dextrose Of the other 2 L one should contain 5 per cent dextrose in water and the other isotonic solution of sodium chloride which can be injected subcutaneously This should be sufficient in the average patient with no severe protein salt or water deficiency In more severely depleted patients 2 L of 5 per cent protein hydrolyzate and 5 per cent glucose should be given instead of 1 and the remaining liter should consist of either isotonic solution of sodium chloride or 5 per cent glucose in water the former having the advantage of being injectable under the skin In cases of most severe protein depletion all 3 L should consist of a 5 per cent amino acid preparation and 5 per cent glucose

Tolerance to Amino Acid Mixtures and Casein Digests Given Intravenously S C Madden R R Woods F W Shull J H. Remington and G H Whipple (*Univ of Rochester) tested several synthetic mixtures* of natural and racemic crystalline amino acids suitable for the daily nitrogen requirement in dogs for their tolerance on intravenous injections Certain mixtures of the 10 essential amino acids plus nonessential amino acids exclusive of glutamic acid were accepted without obvious signs of disturbance even at rates above 10 mg nitrogen per kg per minute for quantities greater than 300 mg per kg One such mixture consisted in parts per 100 of dl threonine 7 dl valine 15 l(—) leucine 10 9 dl isoleucine 9 9 l(+) lysine HCl H O 10 9 dl tryptophane 3 dl phenylalanine 9 9 dl methionine 6 l(+) histidine HCl H O 5 l(+) arginine HCl 5 glycine 9 9 dl α alanine 4 dl serine 2 l(—) cystine 0 5 and l(—) tyrosine 1 In addition other well tolerated mixtures included the prolines

When glutamic acid natural or racemic was included in similar mixtures vomiting frequently occurred at nitrogen rates above 4 mg per kg per minute Vomiting almost always occurred on the first daily injection of a

(7) J E per M d 81 439 448 M y 1945

be done by dissolving them in water, milk or juices Tube *feeding of the amino acids is of special value following* jejunostomy or gastrostomy

For parenteral administration Elman recommends mixture of 5 per cent protein hydrolyzate, 5 per cent glucose and 0 2 per cent sodium chloride, 1 L of such a solution provides water, salt carbohydrate and protein Rate of administration must be governed subjectively and care must be taken to avoid nausea and vomiting two hours is usually required for administration of 1 L in an average sized adult Often the patient may adjust the flow of fluid himself Injections are best given 1 L at a time morning and evening If the injection supplements food by mouth it should be given in the evening or after the last meal so it will not interfere with eating of food Intravenous administration must be done with great care contamination must be specially avoided since a solution of amino acids is an excellent culture medium Pyrogenic reactions may be produced by such contamination When amino acids are injected *subcu*taneously the solution must be isotonic with blood and neutral in reaction A mixture of 5 per cent glucose and 5 per cent amino acids diluted with an equal quantity of distilled water provides isotonicity to achieve maximal absorption and minimal local reaction A larger volume of fluid is needed when given subcutaneously

For acute dehydration up to 5 L of fluid may be needed in parenteral feeding Under certain circum*stances special fluids for treatment of acidosis* and alkalosis also are indicated Plasma or whole blood transfusions may be needed for the acute hypoproteinemia and anemia For surgical and other patients unable to take food by mouth a simple plan of parenteral feeding should be made so that all nutritional elements can be introduced intravenously in a volume of 3,000 cc This amount of water is probably necessary in most cases for maintenance of water balance and for provision of daily urinary output of 1 000 cc or more Of this volume at

that the soy bean is a valuable adjunct to the commoner sources of dietary protein

Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs Carl V Moore Reubenia Dubach Virginia Minnich and Harold K Roberts[4] (Washington Univ) discuss the disagreement between clinical and some animal investigators as to the form in which iron is taken up by the body from the intestinal tract The accurate method of measuring iron absorption by using the radioactive isotope of iron developed by Hahn and his associates was used to solve this problem Studies were made on normal and iron deficient dogs and on normal and iron deficient human subjects Dogs were used because they appear to absorb ferrous iron as easily as ferric iron

From 1 to 4 mg iron per kg body weight was given under fasting conditions The amount of radioactive iron which later appeared as hemoglobin in the peripheral blood was used as the measure of the amount absorbed Human subjects absorbed 1½–15 times more ferrous than ferric iron while dogs either absorbed both forms equally well or showed preferential assimilation of ferrous salts The authors offer three possible explanations for the greater absorption of bivalent iron by the human being (1) only ferrous iron may be absorbed and all trivalent iron may have to be reduced before it can be absorbed (2) both forms may be absorbed but in unequal quantity and (3) ferric iron may be less available for absorption because it readily forms complex insoluble compounds within the intestinal tract

Vitamin Content of Liver Extracts for Parenteral Use Guy W Clark[5] (Pearl River N Y) states that quantitative variations in the several vitamin B factors present in different brands of liver extract for parenteral use are partly due to the different extraction processes employed Since the preformed substances stored in the

(4) J Clin I est gatl 3 755 67 S pt mb 1944
(5) Am J M S 09 5 0-524 Ap l 1945

mixture containing glutamic acid and usually on any subsequent injection of a mixture containing more than 100 mg glutamic acid per kg unless given very slowly Tolerance was improved by addition of glycine to certain mixtures of the 10 essential amino acids Two casein digests tested usually produced vomiting probably because of their glutamic acid content No serious reaction followed injection of any mixture of amino acids or casein digest Elimination of minor reactions such as vomiting appears possible and desirable for greater usefulness of these solutions in parenteral feeding

[Deficiency of serum proteins is a consequence of many bodily disorders and its correction is often vital to recovery Transfusions of blood and blood plasma are usually inadequate and always expensive Amino acid mixtures and protein digests are the answer to our problem The disadvantage of occasional unfavorable reaction following parenteral administration persists Investigations of this nature should result in their eventual elimination —Ed]

Digestibility and Biologic Value of Soy Bean Protein in Whole Soy Beans, Soy Bean Flour and Soy Bean Milk William M Cahill, Lawrence J Schroeder and Arthur H Smith[3] (Wayne Univ) studied these factors of the three soy bean products in adults Little difference was found in the true digestibility of the products the average was 90 5 per cent for the protein in cooked whole soy beans 94 per cent for that in cooked soy bean flour and 89 6 per cent for that in soy bean milk The method of Murlin and his associates which employs the protein of whole egg as a standard, was used to determine average biologic value of soy bean protein for maintenance in adult human subjects This value was found to be 94 5 per cent for the protein in cooked whole soy beans, 91 7 per cent for that in cooked soy bean flour and 95 3 per cent for that in a commercial soy bean milk These high values agree with those reported as observed in animal studies Under the experimental conditions more nitrogen was excreted in the feces when the subjects were fed diets containing soy bean products than when they were fed a standard egg diet It is concluded

(3) J Nut ti n 28 09 18 Sept 11 1944

substances from the original extract and to make an injectable solution From then on the processing steps are different with each manufacturer

[I see no advantage in using the crude extract in the treatment of pernicious anemia but will continue to prefer it in the treatment of sprue hepatic cirrhosis and the deficiency states associated with disorders of the gastro intestinal tract such as gastrojejunocolic fistula —Ed]

Nutritional Recovery Following Removal of All but 3 Ft of Jejunum and Half the Colon is reported by Robert Elman and James Allan Read[6] (Washington Univ)

Man on June 1 1944 was admitted with a draining fecal fistula in the right lower quadrant and complaining of great loss of weight and passage of gas and fecal material through the urethra He had had many previous operations beginning in 19 for regional ileitis with two resections of the ileum He had had no symptoms for over a year Abdominal examination showed moderate distention and a fecal fistula just above the right inguinal ligament The urine contained a good deal of feces There were moderate anemia and hypoproteinemia He had low grade fever Gastro intestinal roentgen examination showed many changes in small and large intestines. The pattern of the small intestine was chaotic and displaced from the right lower quadrant and pelvis without evidence of responsible factors The opaque meal entered a distinct descending colon within two hours of the gastric fill up The ascending colon was recognizable on the motility films showing marked irregularity and poor filling The barium enema canalized to the left side of the transverse colon where there was a funnel shaped narrowing which continued proximally into an irregular smooth and narrow ascending colon The descending colon was hypotonic Cystoscopic examination showed a small contracted bladder with marked cystitis and an indentation at one point undoubtedly due to the abscess in the right lower quadrant Injection of the fistula with lipiodol revealed a connection with the urinary bladder and with various loops of small intestine and a large cavity in the upper part of the pelvis behind the bladder

At first operation on June 15 only 3 ft of normal small intestine was found all the remainder was matted together diseased and ulcerated and damaged beyond recovery at a point distal to the short 3 ft of normal jejunum The colon was normal from the hepatic flexure distally The jejunum was divided at the point where it became diseased its central end was turned in and isoperistaltic side to side anastomosis was made between the jejunum and healthy

(6) J M ssouri M. A. 4 145 146 Ma h 1945

liver are being dealt with the amount of which depends partly on nutrition of the animal, there may be some variations in yields even when the same process is used A comparison of the data on the concentrated extracts with those on the crude extracts may help in evaluating the dilute unrefined preparations

Quantitative analysis of U S P crude and refined liver extracts indicates that on the average, the refined preparations contain as much or more riboflavin niacin pantothenic acid and Lactobacillus casei (Bc) than do the crude preparations There is no evidence that any of the well known B factors is directly involved in hemopoiesis in pernicious anemia Refined concentrated liver extracts are highly effective in control of signs and symptoms associated with this condition. Since investigations have shown that crude extracts contain on the average less riboflavin niacin pantothenic acid and Lactobacillus casei factor than the refined concentrated preparation there is little justification for preferred use of crude liver extract in treatment of Addison s pernicious anemia or as a source of the several B factors

The confusion in definition of crude liver extract should be cleared up now that the first supplement of *United States Pharmacopeia XII* contains a definition of the substance Although each manufacturer of liver extract prepares material corresponding to Cohn s G fraction, there are many modifications which result in differences in color content of total solids, total nitrogen antianemic substance and several components of the B complex One of the steps in general use consists of the addition of sufficient 95 per cent alcohol to a sirupy concentrate of the original water extract to obtain a mixture with 65 per cent alcohol by volume The antianemic substance and varying amounts of the B complex factors stay in solution in this mixture leaving a voluminous tarlike residue which contains the major portion of the B complex factors (extracted by water in the first stage) This step is essential to remove proteins and other inert

[A most pleasing result and one confirming several other recent reports in which a large portion of the small bowel was removed. Surely the human organism has a remarkable power of adaptability —Ed]

Failures in Treatment of Allergy John A Turnbull[7] (Boston) reports a number of cases to illustrate that allergy can be detected and treated properly only by those who have had careful training and long experience in this work who are skilled in interpreting the varied reactions given by different types of skin and who have the patience to give each patient the benefit of all possible sensitizing proteins Turnbull regularly uses 240 different test substances in his cases The patient s co-operation is of primary importance to success of treatment, instructions and diets must be followed rigidly for as long as prescribed The co-operation of other physicians who refer their patients to allergists is another factor of prime importance The referring physicians often modify or nullify the directions given by the allergist and frequently condemn all testing and dieting for protein sensitization thereby undermining the public s confidence and not helping the patients Skin tests properly made with reliable test substances and properly interpreted and precise rules concerning the patient s dietary regimen and environmental regulations strictly followed by the patient will assure the detection and successful treatment of allergy

Synthetic Predigested Aliment for Jejunostomy Feeding Franklin Hollander Stephen Rosenak and Ralph Colp[8] (Mount Sinai Hosp New York City) point out that for jejunal feeding an aliment must be easily digestible or even predigested because salivary and gastric digestion are completely eliminated and pancreatic and intestinal digestion lessened Extensive predigestion is also important for a maximum of absorption Anything irritating to the bowel cannot be contained in the aliment and its pH should be about 6 0 The aliment rec

(7) Am. J D ge t D 11 363 368 N emb 1944
(8) Surgery 17 754 763 M y 1945

transverse colon The remaining central portion of the colon i e, the hepatic flexure was adherent to the rest of the small intestine and could not be mobilized There was an abnormal amount of bleeding from cut tissue although platelet counts and prothrombin time were normal before operation The diseased intestine was left for the time because of the pelvic abscess The wound was closed Recovery was uneventful Postoperative therapy included sulfonamides and penicillin and complete alimentation parenterally with amino acids glucose electrolyt and vitamins backed initially by a transfusion of 1 L whole blood

Nine days later the wound was reopened and the anastomosis located The jejunum had hypertrophied to at least twice its previous size The colon was divided to the right of the anastomosis the distal end turned in and total excision of the remaining colon and small intestine carried out The superior mesenteric artery was isolated and divided Near the pelvis a large abscess was found th contents of which were aspirated The point of attachment between small intestine and urinary bladder was located undoubtedly the site of the fistula into the urinary bladder A catheter passed through the urethra into the bladder permitted distention of the bladder with saline without leakage into the peritoneal cavity The mass of diseased intestine was removed in one piece the wound was closed and through separate incisions the retrocystic space at the site of the urinary fistula as well as the lateral abscess was drained Blood transfusions and intravenous feeding chemotherapy for several days and later careful feeding by mouth aided in uneventful recovery he left the hospital 17 days after the second operation

It was felt that a person with only 3 ft of small intestine and but half of the large bowel might have great diffi ulties in absorption of food However the nutritional status improved steadily, so that after three months he had gained 10 lb He is now on an unrestricted diet eats anything he pleas s three or four times a day and has but two semisolid stools daily Undoubtedly compensatory mechanisms developed during the many years that portions of the small intestine were removed X ray examination three months after discharge showed barium entering the transver e colon near the splenic flexure within two hours of the gastric fill up and to be in the sigmoid flexure in four hours Some barium remained in the small intestine after six hours as would ordinarily be seen At 24 hours a moderate barium concentration was present in the descendin colon and the patient had two formed stools A barium enema demonstrated the d cending colon and refluxed into the small intestine the latter appeared to be jejunum There was therefore good total alimentary tract function without undue hypermotility of the remaining colon and a freely functioning enterocolostomy

drip to patients with complementary jejunostomies and subtotal gastrectomies and one patient with jejunostomy preliminary to gastric resection Sometimes saline solution was added when water and additional salt seemed desirable Rate of administration was 30–60 cc per hour during the first days with gradual increase to around 125 cc per hour All patients receiving the aliment for any significant length of time gave ample evidence of improvement in general nutritive condition and chemistry of tissue fluids Actual diarrhea occurred in only one patient and abdominal cramps in two others one of whom also had cramps when the aliment was not given. Vomiting occurred in three patients but disappeared when the rate of administration was reduced to a more tolerable level Subsequent gradual increase of the rate of drip was always well tolerated and some of the patients were able to take as much as 300 cc per hour without any other reaction except a feeling of fulness

[Various p eparations have been proposed and used but all have some d awbacks This one devi ed by Hollander and his associates shows promise and deser es a good trial by the profess on —Ed]

Laboratory Procedures for Diagnosis of Trichinosis James B McNaught[9] (Stanford Univ) points out the value of laboratory procedures in diagnosis of atypical trichinous infections Diagnosis is established when Trichinella spiralis is found in the blood stool cerebro spinal fluid and muscles Biopsy and autopsy muscle specimens and suspected meat can be examined by one or preferably all of three methods The following is simple rapid and highly satisfactory

TECHNIC —Th n sl ce of fresh material are p essed between two glass sl le and examined microscop ally under a magnification of 10–40 t n es O d nary slides such as are used for blood smears are suitable for soft tis ues but a plate glass type of compressor (Fig 11) is valuable in exam ing larger pieces which may be pressed very thin by tighten ng the thumbscrews All stages of muscle lar ae can be detected by this method Young larvae of the s ze found

(9) Am J Cl P th 14 87 93 S ptemb 1944

ommended by the authors consists of the elements shown in the table

TECHNIC —Amounts of the amino acids carbohydrates and salt mixture sufficient to make 1 L of the diet are weighed out and dissolved in warm tap water without stirring The mixture (volume about 900 cc) is transferred to a milk bottle which is capped and sterilized. After cooling to below 10 C the requisite amount of vitamin preparations is added ascorbic acid being first dissolved in a small amount of sterile water The preparation is kept in the

COMPOSITION OF PREDIGESTED ALIMENT

	AMOUNT PER LITER	AMOUNT PER 2 400 CAL
Water	760 cc	1 8?4 cc
Amigen	85 Gm	204 Gm
Dexin	150 Gm	360 Gm
Cream (18 5 per cent density = 1 01 at 19 C)	85 cc	204 cc
Salt mixture*	10 Gm	24 Gm
Vitamins (min amounts)		
Halibut liver oil†	0 35 cc	0 8 cc
Blexin†	5 8 cc	14 0 cc
Ascorbic acid	63 mg	150 mg

The salt mixtu e s p epa ed n the f llow ng p po t ons

N Cl	100 Gm	4 8 Gm
KCl	100 Gm	4 8 Gm
MgSO 7H O	46 Gm	Gm
Ca glu nate H O	100 Gm	4 8 Gm
Na HPO d d	160 Gm.	7 0 Gm. (cs)

† I ternation l V tam n Co p

refrigerator until required when it is warmed to about body tempera ture and the cream added with vigorous shaking The material is warmed to about 37 C before being placed in the di pensing ap paratus It is administered by a gravity drip apparatus provided with a needle valve at the air inlet to ke p the speed of injection relatively uniform, at an average rate below 200 cc per hour The cream is well emulsified and will not separate if the mixture is gently agitated by air flowing into the drip reservoir through a Mariotte tube If it does separate it can be redistributed by gentle shaking of the reservoir

Dogs given this aliment had no diarrhea or abdominal pain clearly indicating that it is not irritating Loose stools on several occasions were probably due to presence of a contaminating organism in the aliment, which was eliminated by institution of routine daily sterilization of the drip apparatus The aliment was then given by

Diseases in the Tropical War Zones Far East South west and South Pacific Ernest Carroll Faust[1] (Tulane Univ) discusses these nosogeographic regions and their diseases because of their importance in the strategy of the Allied military commands The Far East includes Burma Siam Malaya French Indo China China Korea

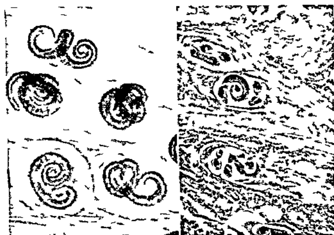


FIG 113 (left) —F h m le p d thin by mp so ed c d f m × 100

FIG 114 (right) —M c o p se t f t ng h w g cy ted l rv e a d m k d my t r du d f m × 100 (M N ght, p 739)

Japan Formosa Philippines Borneo Celebes Sumatra and Java the Southwest consists of New Guinea Solo mons associated island groups and northern Australia the third region includes certain parts of Micronesia of which the Fiji and Samoa groups are of particular im portance

The commonest diseases of this area are malaria many types of enteric infections clonorchiasis paragonimiasis schistosomiasis filariasis kala azar plague the typhus fevers relapsing fever leptospirosis dengue respiratory diseases leprosy smallpox rabies venereal diseases ani mal venenation and malnutrition

(1) G t t l gy 3 163 187 S pt mbe 1944

in the blood and growing larvae can be squeezed from the muscle fiber and identified in the tissue juice at the edges Larger larvae at full length or coiled within the muscle fiber and encysted forms (Fig 113) can be seen. These thin pieces of muscle may be removed from the compressor fixed in formalin dehydrated in alcohol, cleared in xylene and mounted in balsam on a slide with coverslip for permanent record

Skin and precipitin tests are particularly valuable in atypical cases but may be negative in fulminating fatal

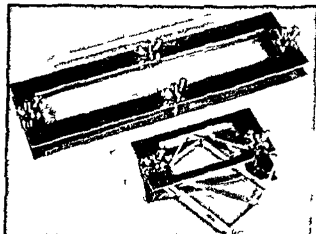


Fig 112 —C mpres s for e amin ng f e h meat for Trichinell p ralis larger is 24 × 8 m (F om Tex s State J Med 38 255 194)

cases McNaught examined 266 persons All but 1 of 36 patients with clinical trichinosis eventually had positive skin reactions of the immediate type The single negative reaction was that of a moribund patient whose diagnosis of trichinosis was later confirmed at autopsy Seventeen of 36 patients for whom trichinosis was a possible diagnosis gave a positive skin reaction Of 194 controls, 6 7 per cent gave positive reactions of the immediate type and 18 1 per cent those of the delayed type The total (24 8 per cent) for this last group was of the same order as that determined by digestion of diaphragms in San Francisco in 1936 Precipitin tests were in almost perfect agreement with the skin reactions

responsible for propagation of the disease Yatren is the most effective drug in treatment Bacillary dysentery the acute type of shigellosis is endemic and usually spread by personal contact it occasionally appears in epidemic form Flexner is the prevailing type in all racial groups Shiga second in Orientals and Sonne second in Occidentals Sulfaguanidine relieves acute symptoms and hastens recovery

Typhoid and paratyphoid fevers are widespread especially in densely populated centers Cholera is endemic in certain centers in Central and South China French Indo China and Malaya and is epidemic during the hot rainy season Sulfaguanidine appears highly specific in treatment but eventual control can be obtained only by public health measures and rigid sanitary disposal of human excreta The helminths which parasitize the native population of the Far East and the Pacific areas are legion and hookworm infection is extensively distributed throughout the entire area Since the infective stage larvae develop from eggs deposited in human feces on the soil and since exposure commonly results from stepping barefooted on the polluted ground the problem of control resolves itself into mass anthelmintic medication and disposal of human excreta Ascariasis due to Ascaris lumbricoides is possibly even more widespread than hookworm infection throughout the Orient and tropical Pacific islands but the victims are mostly young children Clonorchiasis an infection produced by the Chinese liver fluke and paragonimiasis lung fluke infection both widely distributed are acquired from ingestion of infected foods Schistosomiasis and two types of filariasis develop after skin exposure In China more than 100 000 000 people live in territory endemic for schistosomiasis and several millions are affected No water suspected of harboring Schistosoma japonicum should be used for external or internal purposes until it has been boiled adequately filtered or chemically sterilized or has stood for 48 hours or more in a snail free

Malaria is endemic throughout practically the entire eastern Oriental and tropical Australian regions, but is not established in the South Pacific (Fig 115) It is most prevalent in the Far East just before the summer monsoons and again in late summer and early fall The pre

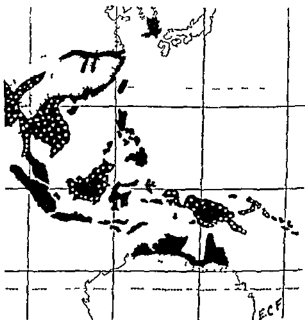


Fig 115.—Dist ibuti n of mal ria in F East and Southwe t P cific Ar of high e dem c ty i sol d bla k (5–75 d th pe 100 000 population) a eas w th wh te d ts sol d bl k nd ate ate of 75 m re deaths per 100 000 a e s of l ght dem c ty stippl d in bl k (o g l)

vailing types are falciparum and vivax The former is responsible for most malaria deaths chiefly because of cerebral complications The latter is of the relapsing form with sapping of energy constituting a major problem for military personnel

Amebiasis is widely distributed and in many regions is highly endemic frank amebic dysentery is however, relatively infrequent in the more temperate climates farther north Insanitary disposal of human excreta is

months in Pacific islands in or near the jungle and in close proximity to the natives Estimation of average in cubation period was fairly difficult but appeared to be between 8 and 16 months with a history of attacks as early as three months A mild constitutional reaction de veloped at the beginning only two patients had chills fever malaise and headache First symptoms largely local were pain swelling or redness of arm or leg or pain and swelling in the scrotal region Symptoms which must be stressed are tendency toward recurrences lack of severe constitutional reactions characteristic lym phangitis of the extremity or genitalia and adenopathy particularly in the epitrochlear region Lymphangitis occurred as many as six times in one patient The com monest lesion was inflammation of the spermatic cord epididymis testis or scrotum or combined involvement of more than one intrascrotal structure this was seen in 192 patients Some lymph node enlargement was found in 228 cases with the epitrochlear region most commonly involved Eosinophilia was present in about two thirds of the patients the cells were invariably mature White blood cell count was normal in two thirds of the cases but significantly elevated in nearly one third There was no fever with this elevation which often persisted for several days and even a few weeks Search for micro filaria was entirely negative Clinical diagnosis is fairly easy and is confirmed by a positive intradermal reaction The intradermal reaction with Dirofilaria immitis anti gen was positive in 90 8 per cent of patients and in 10 5 per cent of a comparable number of controls who had never been in the tropics Experiments with various strengths of antigen showed that a high percentage of individuals may be sensitive to the filarial protein if enough is introduced but that patients with clinical filariasis will react to much smaller doses

Therapeutically no single drug is effective Treatment has been almost entirely symptomatic consisting of rest until the acute symptoms become quiescent and evacua

tank For permanent control, adequate sewage disposal is needed

Kala azar is confined to China and Manchuria, it is amenable to antimony therapy Plague is fairly wide spread and occurs sporadically in epidemic form In North China and Manchuria it has been fairly well con trolled for more than 20 years The four types of typhus fevers are epidemic typhus, prevalent in the northern countries of the Far East, murine typhus, appearing throughout the Far East scrub typhus, prevalent in Japan Formosa Malaya and Australia, and Q fever endemic in northern Queensland Relapsing fever is endemic throughout the Maritime Provinces of the U S S R, Manchuria, Korea, Japan and China down to Indo China The spirochete is transmitted by the louse The various forms of leptospirosis are extensively distributed through the Far East and the Australian area Dengue is the most widely distributed endemic disease of the entire area Yellow fever has not occurred in the area during historical time The more important respira tory diseases are prevalent throughout the area as is leprosy, which is correlated with poverty crowding and poor sanitation Venereal diseases syphilis and gonococcic infection are widespread appearing in 10-50 per cent of the population Among the venenating and poi sonous animals are the various arthropods, such as mosquitoes fleas and the like, scorpions venomous snakes and various types of fish

Tremendous work awaits the medical departments of the military forces in instituting medical and sanitary rehabilitation of the liberated peoples, and physicians in the United States will have a major problem in deal ing with the various tropical diseases developing in re turning military personnel

Early Filariasis Diagnosis and Clinical Findings Boyd G King[2] (Fourth Gen l Hosp) reports on 268 cases in American troops, who lived an average of four

(2) Am J Trop Med 24 285 298 September 1944

appeared only after some weeks usually associated with changes in the scrotal contents Pain often disappeared when the scrotal swelling became maximal Many patients had severe malaise cold sweats and nervousness Involvement of superficial lymph nodes and vessels was less common if present it was associated with pain tenderness and swelling Lymphangitis always spread peripherally Cellulitis occurring in the thigh usually was confined to the upper inner third Pain on walking was often present Both symptoms and swellings were aggravated by exertion and on hot humid days rest and cool weather had the opposite effect In most cases an interval of freedom from symptoms followed but acute episodes recurred from one to three months later and were then increasingly severe and persistent



FIG 116 —N t w th se- gu l lymph d op thy d t fil n

The vector is considered to be Aedes scutellaris a species accounting for 95 per cent of the large mosquito population of the island Diagnosis of the disease was not possible at first Later as well marked lesions developed and the number of patients increased the presence of microfilarias in the blood of a high percentage of natives together with a high density of a known vector led to a tentative diagnosis of filariasis This could not be proved because of absence of microfilarias or adult worms in the patients

The only treatment is symptomatic Bed rest and occasional sedation were found to be the most effective measures Severe pain and swelling of the spermatic cord

tion of most patients to prevent recurrences Prophylactically mosquito control is the ideal procedure practiced both day and night because of the day time biting habits of Aedes variegatus the chief vector in the Pacific Islands east of the New Hebrides group

Filariasis in Soldiers on a South Pacific Island Theodore D Englehorn and William E Wellman[3] describe the clinical picture in 127 American soldiers This picture is that of early filariasis and knowledge of it will aid in early clinical diagnosis of the condition Comparison with natives with long standing filariasis was also possible

The shortest time after exposure at which symptoms definitely attributable to filariasis appeared was three months In most cases mild symptoms appeared in five months and more severe symptoms in eight months In some cases it was 14 months before symptoms appeared Early undiagnosable symptoms included anorexia nausea and vomiting and pain of variable and remarkable distribution to the back suprapubic region, groin spermatic cord testes and inside of the thighs Severity of symptoms varied greatly In general the more severe the early symptoms the more marked the latter manifestations Further developments occurred usually 10–14 days after the first symptoms and consisted mostly of involvement of the scrotal contents this occurred in 75 per cent of patients Also present was involvement of superficial lymph vessels and nodes of arm or leg The first physical finding was often acute epididymitis with swelling and tenderness of the upper pole sometimes of the whole organ The most frequent abnormality was acute funiculitis There was usually marked tenderness over the inguinal canal Swelling of the spermatic cord was present early Varicoceles developed temporarily in some patients with funiculitis Tense swelling of the testis to twice its usual size was common Generalized scrotal swelling with soft boggy thickening of the wall

(3) Am J M Sc 209 141 15 February 1945

[This disorder has caused much apprehension in soldiers and their immediate relatives because of the possibility of infertility from involvement of the genitals and unsightly disfigurement from swellings or elephantiasis However as the result of extensive investigations conducted by the Army and Navy such fear appears to be groundless if the affected soldier is evacuated early from the endemic area and future exposure avoided. And chances for infection of the civilian population is slim even though the vector is harbored in various parts of the United States So far no specific remedial agent has been found.—Ed]

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and scrotal contents were treated with some success by elevation and application of an icecap Acute lymphangitis was treated by elevation of arm or leg and application of hot moist compresses Sulfadiazine was of no benefit Between acute attacks limitation of physical exertion was necessary and beneficial Reassurance of the patients is important because of their familiarity with

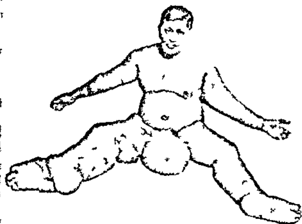


Fig 117 —Native 44 with severe elephantiasis of scrotum and legs

elephantiasis in natives Patients with diagnoses of filariasis were evacuated to the United States unless they develop microfilarias in the circulating blood they cannot be regarded as a source of infection for others Prognosis cannot be stated with certainty but may be quite hopeful Early removal of infected soldiers from endemic areas and careful avoidance of reinfection may protect them at least in most cases from the late manifestations Mosquito control is the only satisfactory solution of the problem if that is impossible, prolonged exposure in endemic areas should be avoided

Examination of natives on the island showed that 40 per cent of those examined by blood smear had microfilarias, at least 5 per cent had elephantiasis

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